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THIAZOLES IN ORGANIC SYNTHESIS. NOVEL SYNTHESES OF MENTHANES AND EREMOPHILANES §

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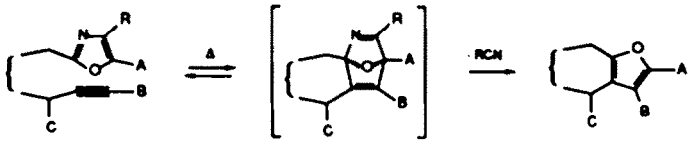
Abstract: Acetylenic thiazoles of proper design have been shown to undergo an intramolecular Diels-Alder reaction leading to fused-ring thiophene derivatives. When appropriately substituted, these latter materials can be readily converted to terpenes of the menthane and eremophilane class by Raney-nickel desulfurization.

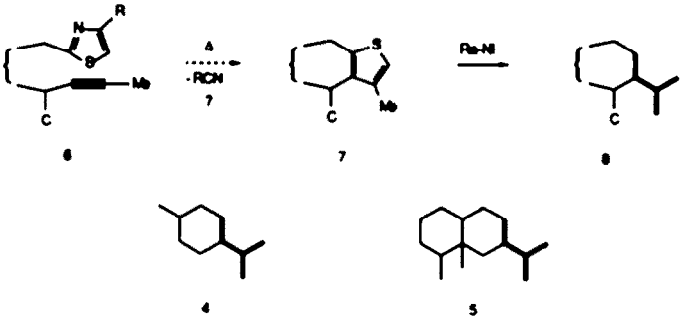
Introduction

For several years now we have been developing a general synthetic approach to the highly oxygenated sesquiterpenes, the most notable feature of which is the use of an intramolecular Diels-Alder reaction of an acetylenic oxazole to generate a fused furan ring.[1] This approach is of particular utility for the preparation of highly substituted furans, since substituents of the type A, B and C are transposed in an unequivocal fashion through intermediate 2 to the final adduct 3.



1 2 3

As an extension of this methodology, we were interested in the possibility that thiazoles of type 6 might be directly converted to fused-ring thiophenes of type 7 by a pathway analogous to that shown for the oxazole counterpart 1 (Figure 1). Such a transformation could be of considerable practical importance, since in principle, 7 might be further converted to isopropyl derivatives of type 8 by Raney nickel hydrogenolysis.[2,3] Substitution patterns of the type generalized in 8 are exceedingly common in nature, especially in compounds derived *via* an isoprene biosynthetic pathway [*cf.*, for example, the menthane (4) and eremophilane (5) classes of terpenes].



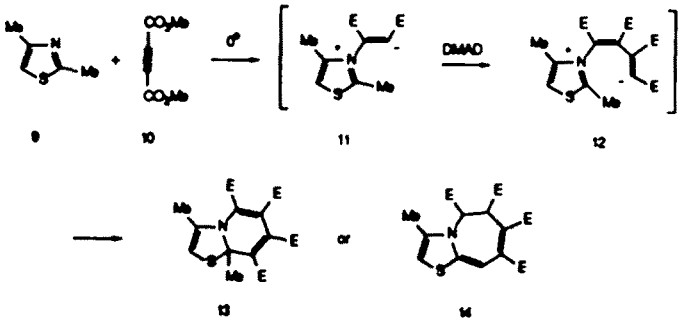
6 7 8

4 5

Figure 1

An obvious difficulty with this strategy is the low reactivity of thiazoles in Diels-Alder reactions.[4,5] This lack of reactivity is partly due to the greater aromaticity of thiazoles relative to oxazoles,[4] as well as to the high nucleophilicity of the thiazole ring.[6,7] For example, 2,4-dimethylthiazole (9) reacts at 0° C with dimethyl acetylenedicarboxylate (10) to give the Michael adduct 11, which subsequently adds a second molecule of 10 to afford the zwitterionic species 12 (Scheme 1). In DMF as solvent, 12 collapses directly to the annulated product 13, while in THF 12 undergoes an initial 1,5-hydrogen atom transfer, followed by cyclization to the azepine derivative 14.[7] In spite of these results, however, we were hopeful that entropy factors might contribute to a more favorable outcome in the intramolecular Diels-Alder cyclization.

§ Dedicated to my good friend and mentor, Professor Edward C. Taylor, on the occasion of his 65th birthday.

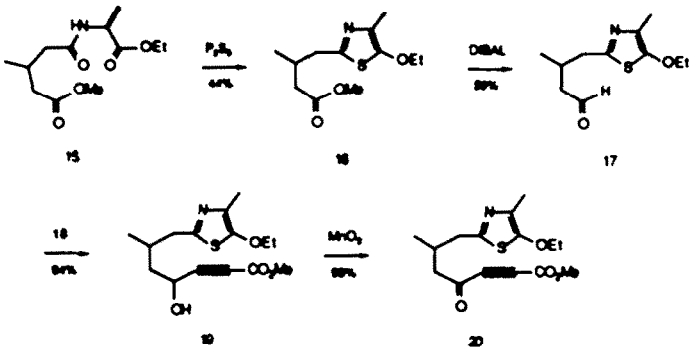


Scheme 1

Results and Discussion

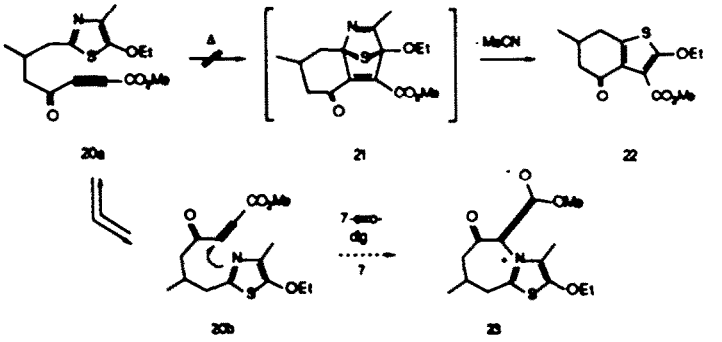
(a) Model Studies; Geometrical Control of Reaction Pathway

Our initial studies were carried out with the acetylenic esters **19** and **20**, which were conveniently prepared as diagrammed in Scheme 2 (*cf.* experimental section). Upon warming, **20** rapidly decomposed to an intractable mixture



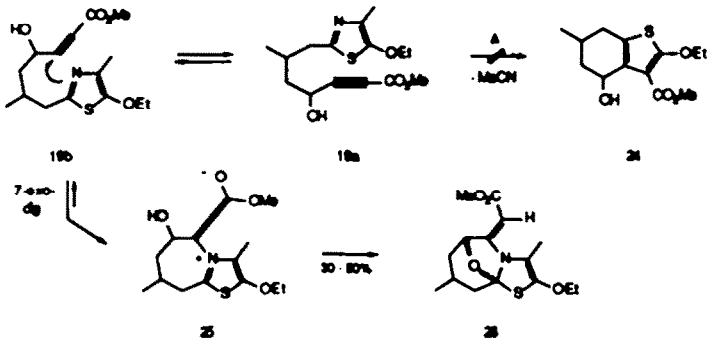
Scheme 2

which contained none of the desired thiophene ketone **22**, and which showed no evidence for the initial formation of the Diels-Alder adduct **21** (Scheme 3). This instability is most likely due to the rapid formation of the Michael adduct **23**, in exact analogy to the intermolecular examples provided in Scheme 1. Models indicate that the 7-*exo-dig* transition state leading from conformation **20b** to **23** should be highly favored,[9] and once formed, **23** might decompose by a variety of reaction pathways.



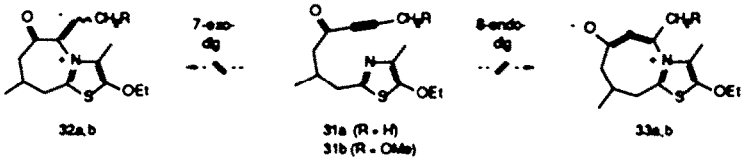
Scheme 3

These suspicions were confirmed upon thermolysis of the acetylenic alcohol **19** (Scheme 4). Once again, we found no evidence for the formation of the desired thiophene alcohol **24**. However, in this case the initial Michael adduct **25** was further transformed to the ortho ester derivative **26**, which was isolated in 30-50% yield as an unstable crystalline solid. In addition to mechanistic considerations (*vide supra*),[7] the assigned structure for **26** is based upon extensive spectral analysis and careful comparison with suitable model systems.[1d,10-12]

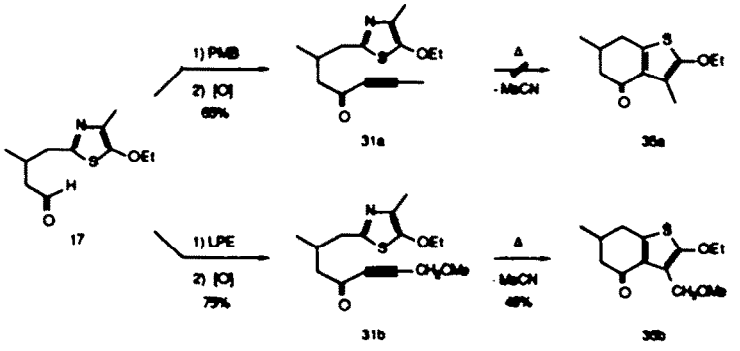


Scheme 4

Several alternatives were available for circumventing the intramolecular Michael addition. As one possibility, it seemed likely that thiazoles of type **31a** and **31b** should be less reactive toward the 7-*exo-dig* process, since the resulting anions **32a** and **32b** are not stabilized by delocalization. Furthermore, the alternative 8-*endo-dig* cyclizations, proceeding through allenolates **33a** and **33b**, are geometrically unfavorable.



Thiazole **31a** was readily prepared by condensation of aldehyde **17** with propynylmagnesium bromide (PMB), followed by oxidation of the resulting acetylenic alcohol **34** with Swern's reagent (Scheme 5).[13] In analogous fashion, **31b** was derived by condensation of **17** with lithiomethyl propargyl ether (LPE) and subsequent oxidation. Both **31a** and **31b** were then subjected to thermolysis under a variety of conditions. Thiazole **31a** suffered mainly slow

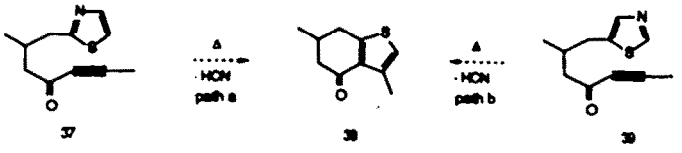


Scheme 5

decomposition to polar products over a period of several days in refluxing ethylbenzene (~136° C), and all attempts at catalysis either had no effect (BF_3-Et_2O, $Hg(OAc)_2$, TsOH, $ZnCl_2$), or led to addition reactions at the acetylenic triple bond ($AlCl_3$).[14] Also, higher temperatures gave rise to rapid decomposition which could not be controlled by the addition of various radical scavengers.[15] With thiazole **31b**, however, the additional activating influence of a methoxy group apparently facilitates the Diels-Alder process. In the presence of a catalytic amount of methylene blue,[16] **31b** gave a 48% yield of thiophene **35b** after three days at reflux in degassed mesitylene (~165°, 62% yield of **35b** based on recovered **31b**). This example provided the first evidence that thiazoles can undergo the Diels-Alder reaction with acetylenic dienophiles in exactly analogous fashion as their oxazole counterparts.

(b) α- and β-Menthanes

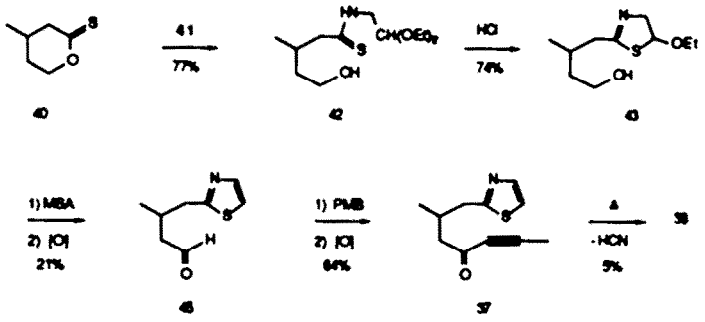
We next turned our attention to the preparation of the thiophene ketone **38**, a material which could serve as a precursor for the synthesis of members of the menthane (**4**) class of monoterpenes (Scheme 6). In principle, **38** was derivable by thermolysis of either the 2-substituted thiazole derivative **37** (*path a*), or the 5-substituted thiazole **39** (*path b*). Each of these routes had certain advantages. For example, it seemed likely that **37** could be prepared by methodology similar to



Scheme 6

that employed in the preceeding section (*cf.* Schemes 2 and 5), while **39** would most likely require the development of new methodology. On the other hand, in **39** the nucleophilic ring nitrogen is in an inaccessible position relative to the acetylenic π-bond, and therefore an intramolecular Michael addition is impossible.

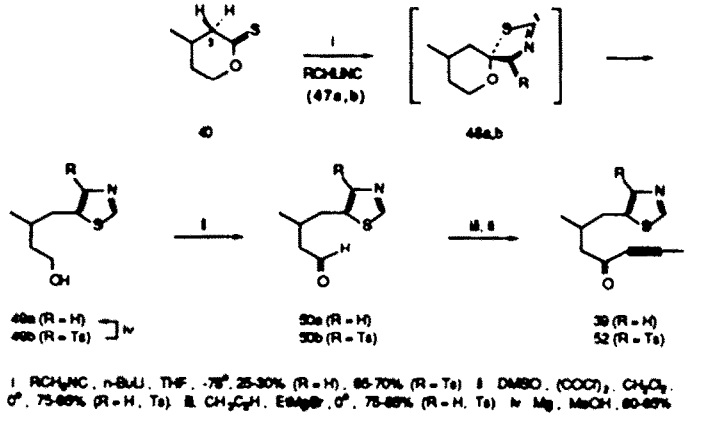
The key intermediate for our synthesis of **37** was the thiazole aldehyde **45**, which was routinely derived, albeit in modest overall yield, from the readily available thionolactone **40** (Scheme 7). Thus, reaction of **40** with aminoacetaldehyde diethylacetal (**41**) gave a 75-90% yield of the thioamide derivative **42**, which was directly cyclized to the Δ-2-thiazoline **43** following the general procedure of Lawson.[17] At this stage we encountered unexpected difficulties



Scheme 7

in effecting the elimination of a second molecule of ethanol. However, after extensive experimentation, we found that methanesulfonic acid (MSA) brought about the crucial aromatization step in 30-40% yield,[18] and the resulting thiazole alcohol **44** was smoothly oxidized to the desired aldehyde **45** using Swern's reagent.[13] This last material then gave the target acetylenic ketone **37** upon condensation with propynylmagnesium bromide (PMB) followed by oxidation (*cf.* also Scheme 5).[13] To our disappointment, however, **37** was extremely unreactive in the Diels-Alder reaction. The best results were obtained at 240° C, whereupon **37** afforded a 5% yield of the desired thiophene **38** along with extensive decomposition.

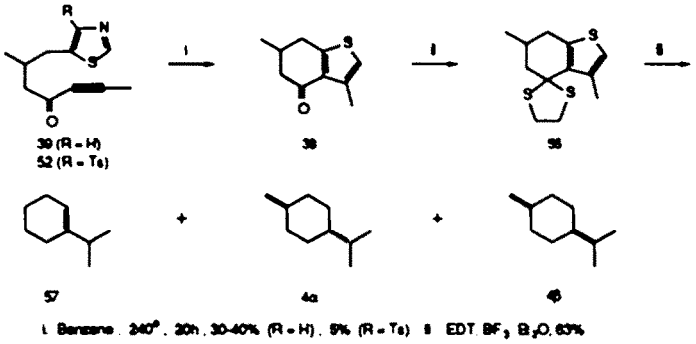
Our initial experiments for the synthesis of **39** were based upon a modified Schöllkopf reaction of the thionolactone **40** with lithiomethylisocyanide (**47a**) (R=H) (Scheme 8).[19] We anticipated that **47a** would readily add to the highly electrophilic C=S bond in **40** to provide the Δ-2-thiozoline anion **48a** (R=H) after intramolecular cyclization. Subsequent proton transfer and aromatization would then yield the desired thiazole alcohol **49a**. In practice, however, yields of **49a**



Scheme 8

were disappointingly low following this direct procedure (< 30%), apparently due to competing proton abstraction at C-3. In contrast, the much less basic reagent **47b** (R=tosyl) reacted smoothly with **40** to provide the thiazole alcohol **49b** in 65-70% yield with no competing side reactions. Once in hand, **49b** could be cleanly converted to **49a** by reductive cleavage with magnesium in methanol,[20] and both **49a** and **49b** were then carried on to the respective acetylenic ketones **39** and **52** by a sequence of reactions involving Swern oxidation to the aldehydes **50a** and **50b** (75-95%),[13] followed by condensation with propynylmagnesium bromide and re-oxidation (75-85%).

Not surprisingly, thiazole **52** was relatively unreactive in all attempts at conversion to the thiophene ketone **38**, affording the desired compound in only 5% yield after 20 h at 240° C (benzene, sealed tube) (Scheme 9). In this case the electron withdrawing tosyl group at C-4 undoubtedly exerts a deactivating influence. Under these same conditions, however, thiazole **39** afforded a 30-40% yield of **38** with substantially less decomposition than observed with either **52** or **37**. Although not optimized, these experiments provided sufficient quantities of **38** for further study. We hoped that



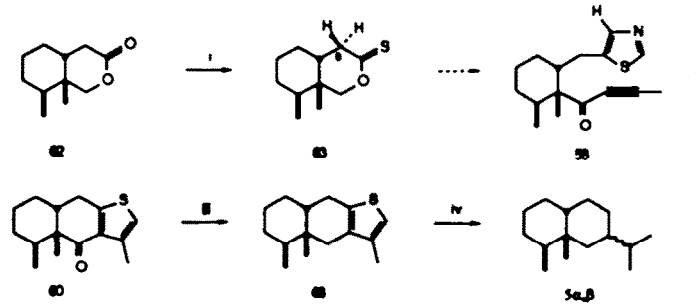
I. Benzene, 240°, 20h, 30-40% (R = H), 5% (R = Ts) II. EDT, BF_3, Et_2O, 63%
III. W-7 Ra-Ni, EtOH/hexane, 99%, 57 4α 4β = 1 52 47

Scheme 9

38 could be directly reduced to compounds of the menthane (**4**) class of monoterpenes by Raney-nickel desulfurization.[2] However, all attempts in this direction led to complex mixtures of products which appeared to contain both α- and β-menthone, as well as various menthol derivatives. More satisfactory results were realized upon reduction of the thioketal derivative **56**, which was routinely prepared from **38** with ethanedithiol/BF_3·Et_2O. In this case we obtained a 99% yield of the menthanes **4α** and **4β** (52:47) in addition to trace amounts (~ 1%) of the menthene derivative **57**.

(c) α- and β-Eremophilones and -Eremophilanes

By analogy, we expected that the acetylenic thiazole **58** would serve as an efficient precursor for the thiophene ketone **60** (Scheme 10). With **58**, as compared to **39**, the diene and dienophilic portions of the molecule are held in close proximity to each other, and the entropy change in proceeding from **58** to **60** should be more favorable. Once in hand, it was our hope that **60** could be reductively cleaved in such a fashion as to provide the eremophilanes **5α** and/or **5β**.[21] The starting point for our synthesis of **58** was the thionolactone **63**, which was derived in 70-85% yield by treatment of the known oxygen analogue **62**[1a] with Lawesson's reagent.[22] Lactone **63** was then readily converted to **58** by an identical procedure as that employed in the synthesis of **39** (*cf.* experimental section, 63 --> 65b --> 65a --> 66 --> 67 --> 58).[23] Next, we were gratified to find that **58** gave an 81% yield of the desired thiophene ketone **60** upon thermolysis in decalin, and finally, **60** could be cleanly reduced to the saturated analogue **68** with LAH/$AlCl_3$. On the basis of literature

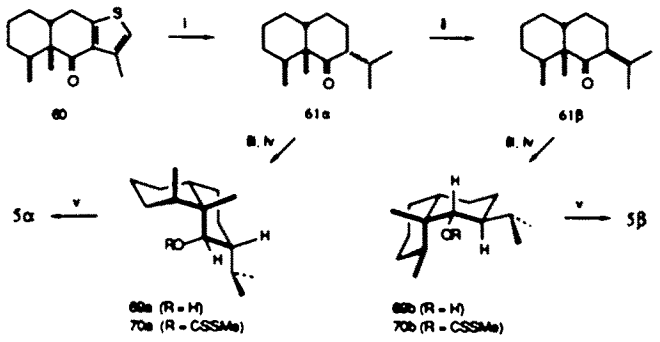


I. $(MeODPS)_{2Ti}$, 70-85%. II. 325°, 81%. III. LAH / $AlCl_3$ (1 : 2), 94%. IV. W-7 Ra-Ni, 87%, 1 : 1

Scheme 10

precedent this last material was expected to be an ideal precursor for 7-α-eremophilane (5α).[24] This turned out not to be the case, however, since Raney-nickel cleavage of **6β** consistently gave ~ 1:1 mixtures of 5α and 5β, albeit in excellent overall yield.

Much better results were obtained following the approach outlined in Scheme 11. Thus, **60** gave a 91% yield of the isopropyl ketone **61α**, contaminated with < 5% of the isomeric material **61β**, upon reductive cleavage with W-7 Raney nickel. Compound **61α**, in turn, could be quantitatively epimerized to the thermodynamically more stable **61β** upon equilibration with NaOMe/MeOH. Each of these materials was then carried on separately to the corresponding



I. W-7 Ra-Ni, hexanes, 91% (> 95 : 5); II. NaOMe/MeOH, 95 - 99% (> 98 : 2); III. LAH, Et_2O/THF, RT, 80 - 90%; IV. NaH, imidazole, CS_2, MeI, THF, Δ, 80%; V. K metal, t-$BuNH_2$, 18-crown-6, RT, 50%

Scheme 11

hydrocarbons 5α and 5β by initial reduction to the α-alcohols **69a,b** (LAH, 80-90%), followed by conversion to the xanthates **70a,b** and cleavage with K/t-$BuNH_2$ (> 80% yield, GC; 50% isolated).[25] The relative stereochemistry at C-6 for **69a** and **69b** was readily deduced from the H_6 - H_7 NMR coupling constants ($J_{6,7}$ = 2.3 Hz for **69a**; $J_{6,7}$ = 11.2 Hz for **69b**), and in addition, the NMR and IR spectra for 5β were identical with those of an authentic sample.[26]

In closing, we believe that the described methodology could find considerable utility in the synthesis of related sesquiterpene ketones, alcohols, and hydrocarbons when more traditional methods of functionalization are impractical.[27]

Experimental

2-(3-Carbomethoxy-2-methylpropyl)-4-methyl-5-ethoxythiazole (16). A total of 15.4 g (0.070 mol, 4.5 eq) of P_2S_5 was added in small portions to a vigorously stirred solution of 4.01 g (0.016 mol) of ethyl-N-(4-carbomethoxy-3-methylbutyryl)-L-alaninate (**15**)[1c] in 200 ml of $CHCl_3$ maintained at 45° C with protection from moisture. Following addition, the reaction was heated under reflux for a total of 24 h, and then cooled to RT, washed with 20% aqueous KOH, and extracted with 3 x 30 ml of $CHCl_3$. The combined extracts were filtered through celite, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a yellow oil. Chromatography on silica gel then gave 1.76 g (44%) of **16** as a light yellow oil, Rf 0.43 (25% acetone/hexanes). Mass spectrum, m/e 257 (M^+); IR($CHCl_3$) 1725, 1570 cm^{-1}; NMR($CDCl_3$) δ 0.97 (d, 3H, J = 6 Hz), 1.33 (t, 3H, J = 7 Hz), 2.18 (s, 3H), 2.39 (m, 3H), 2.74 (t, 2H, J = 7 Hz), 3.64 (s, 3H), 4.03 (q, 2H, J = 7 Hz). **Anal.** Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.24; N, 5.30.

2-(2-Methyl-4-oxobutyl)-4-methyl-5-ethoxythiazole (17). A solution of 1.00 g (3.89 mmol) of thiazole **16** in 15 ml of dry toluene was cooled to -78° C in a flame dried flask under a blanket of nitrogen. A total of 5.14 ml (2.0 eq) of 25% DIBAL in toluene was then added in dropwise fashion, with vigorous stirring, over a period of 45 min while maintaining a temperature of -78° C. Stirring was continued for an additional 45 min before quenching with absolute EtOH (30 min at -78° C) and then saturated NH_4Cl. The resulting mixture was extracted with 3 x 20 ml of CH_2Cl_2, and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressue to afford a yellow oil. Chromatography on silica gel then gave 497 mg (56%) of **17** as a light yellow oil, Rf 0.38 (25% acetone/hexanes). Mass spectrum, m/e 228 (M^+); IR($CHCl_3$) 1725, 1570 cm^{-1}; NMR($CDCl_3$) δ 0.97 (d, 3H, J = 6 Hz), 1.38 (t, 3H, J = 7 Hz), 2.24 (s, 3H), 2.35 (m, 1H), 2.55 (m, 2H), 2.80 (d, 2H, J = 7 Hz), 4.04 (q, 2H, J = 7 Hz), 9.79 (br s, 1H).

2-(2-Methyl-4-hydroxy-6-carbomethoxy-5-hexynyl)-4-methyl-5-ethoxythiazole (19). A solution of 0.091 ml (1.02 mmol, 1.25 eq) of methyl propiolate in 10 ml of 4:1:1 dry THF/ethyl ether/pentane was cooled to -120° C in a flame dried flask under an atmosphere of nitrogen (the cooling bath consisted of a 4:1:1 mixture of low boiling petroleum ether/acetone/isopropyl alcohol with liquid nitrogen). A total of 0.76 ml (1.25 eq) of 1.35 M n-butyllithium in hexane was then added in dropwise fashion, with vigorous stirring, over a period of 15 min while maintaining a temperature of -120° C. Stirring was continued for an additional 10 min to complete the formation of lithio methyl propiolate (**18**). A solution of 187 mg (0.82 mmol) of aldehyde **17** in 10 ml of 4:1:1 THF/ethyl ether/pentane was then added dropwise with vigorous stirring. The mixture was stirred for 15 min at -120° C, and the cooling bath was then removed. After warming to -78° C, the reaction was quenched with 10 ml of 10% aqueous KH_2PO_4, washed with 20 ml of H_2O, and extracted with 3 x 20 ml of Et_2O. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Chromatography on silica gel then gave 240 mg (94%) of **19** as a light yellow oil, Rf 0.29 (30% acetone/hexanes) (~ 9:1 diastereomeric mixture). Mass spectrum, m/e 311 (M^+); IR($CHCl_3$) 3590 (w), 2225, 1710, 1570 cm^{-1}; UV(CH_3CN) λ_{max} 261 nm. NMR($CDCl_3$) (major isomer) δ 1.02 (d, 3H, J = 6 Hz), 1.37 (t, 3H, J = 7 Hz), 1.84 (m, 2H), 2.21 (s, 3H), 2.28 (m, 1H), 2.85 (m, 2H), 3.75 (s, 3H), 4.03 (q, 2H, J = 7 Hz), 4.60 (m, 1H).

2-(2-Methyl-4-oxo-6-carbomethoxy-5-hexynyl)-4-methyl-5-ethoxythiazole (20). A solution of 52 mg (0.17 mmol) of acetylenic alcohol **19** in 10 ml of dry CH_2Cl_2 was treated with 580 mg (40 eq) of active MnO_2. After stirring vigorously at RT for 15 min, the mixture was filtered through celite, and the celite was washed thoroughly with CH_2Cl_2. The combined washings were concentrated under reduced pressure to give a quantitative yield of **20** as a yellow oil, Rf 0.41 (25% acetone/hexanes). This material decomposed slowly in solution at RT and rapidly on concentration or chromatography. IR($CHCl_3$) 2240, 1724, 1690, 1573 cm^{-1}; NMR($CDCl_3$) δ 1.03 (d, 3H, J = 6 Hz), 1.37 (t, 3H, J = 7 Hz), 2.22 (s, 3H), 2.54 (m, 3H), 2.79 (m, 2H), 3.85 (s, 3H), 4.04 (q, 2H, J = 7 Hz).

Thiazoline 26. A solution of 280 mg (0.90 mmol) of acetylenic alcohol **19** and 18 mg (0.20 eq) of hydroquinone in 10 ml of freshly distilled (Na) ethyl benzene was heated at reflux, with exclusion of light and air, for a period of three hours. The ethyl benzene was then removed under reduced pressure to give crude **26** as an orange-brown crystalline residue. Repeated preparative TLC of this residue afforded a 30-50% yield of **26** as a colorless, crystalline solid, Rf 0.60 (20% acetone/hexanes). Mass spectrum, m/e 311 (M^+); IR($CHCl_3$) 1690, 1605 cm^{-1}, no hydroxyl or acetylenic absorptions; ^1H NMR($CDCl_3$) δ 0.95 (d, 3H, J = 6 Hz, collapsing to a singlet upon irradiation at 1.96), 1.28 (t, 3H, J = 7 Hz, collapsing to a singlet upon irradiation at 3.86), 1.46-1.80 (br m, 2H), 1.96 (m, 1H, *H-8*), 2.12 (s, 3H), 2.24 (m, 2H, *H-9's*), 3.66 (s, 3H, *-OMe*), 3.86 (q, 2H, J = 7 Hz, collapsing to a singlet upon irradiation at 1.28), 5.29 (d, 1H, J = 0.5 Hz, collapsing to a sharp singlet upon irradiation at 5.91, *H-15*), 5.91 (br s, 1H, collapsing to a doublet, J = 3 Hz, upon irradiation at 1.74 and sharpening upon irradiation at 1.60, *H-6*); ^{13}C NMR($CDCl_3$) 11.8 (q, C-14), 14.9 (q, C-13), 20.8 (q, C-11), 25.1 (d, C-8), 33.5 (t, C-7), 46.6 (t, C-9), 50.7 (q, C-17), 69.5 (t, C-12), 81.4 (d, C-6), 84.6 (d, C-15), 110.3 (s, C-10), 114.7 (s, C-3), 137.5 (s, C-2), 159.2 (s, C-5), 167.9 (s, C-16). The analytical sample crystallized from ether/pet ether in the form of colorless needles, mp 90-92° C, which, however, rapidly decomposed at ambient temperatures and were unsuitable for X-ray analysis. **Anal.** Calcd for $C_{15}H_{21}NO_4S$: C, 57.84; H, 6.79; N, 4.52. Found: C, 57.59; H, 6.87; N, 4.23.

2-(2-Methyl-4-hydroxy-5-heptynyl)-4-methyl-5-ethoxythiazole (34). Propyne gas was slowly bubbled into a stirring solution of 0.91 ml of 2.00 M EtMgBr in 15 ml of dry THF under an atmosphere of nitrogen. After a total of 15 min, the propynyl magnesium bromide thus generated was added in a dropwise fashion, *via* a double tipped needle, to a stirring solution of 235 mg (1.10 mmol) of aldehyde **17** in 20 ml of dry THF maintained at 0° C. After addition was complete, the reaction mixture was allowed to stir for an additional 30 min at 0° C, before warming to RT and quenching with 15 ml of saturated aqueous NH_4Cl. The resulting mixture was extracted with 3 x 20 ml of Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Chromatography on silica gel then gave 295 mg (82%) of **34** as a pale yellow oil, Rf 0.27 (25% acetone/hexanes). Mass spectrum, m/e 268 (M^+); IR($CHCl_3$) 3540, 2220 cm^{-1}; NMR($CDCl_3$) δ 1.02 (d, 3H, J = 6 Hz), 1.36 (t, 3H, J = 7 Hz), 1.66 (m, 2H), 2.12 (m, 1H), 2.21 (s, 3H), 2.81 (m, 2H), 4.02 (q, 2H, J = 7 Hz), 4.32 (m, 1H).

2-(2-Methyl-4-oxo-5-heptynyl)-4-methyl-5-ethoxythiazole (31a). This material was prepared from the acetylenic alcohol **34** in 80% yield following the general procedure of Swern *et al.*[13] The acetylenic ketone **31a** was isolated as a pale yellow oil, Rf 0.33 (25% acetone/hexanes). Mass spectrum, m/e 266 (M^+); IR($CHCl_3$) 2223, 1665, 1570 cm^{-1}; NMR($CDCl_3$) δ 1.02 (d, 3H, J = 6 Hz), 1.39 (t, 3H, J = 7 Hz), 2.03 (s, 3H), 2.24 (s, 3H), 2.54 (m, 1H), 2.68 (dd, 2H, J = 13, 4 Hz), 2.79 (t, 2H, J = 7 Hz), 4.05 (q, 2H, J = 7 Hz). **Anal.** Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.36; H, 7.43; N, 5.97.

2-(2-Methyl-4-hydroxy-7-methoxy-5-heptynyl)-4-methyl-5-ethoxythiazole (36). A solution of 0.21 ml (2.44 mmol, 1.25 eq) of methyl propargyl ether in 20 ml of dry THF was cooled to -78° C in a flame dried flask under an atmosphere of nitrogen. A total of 1.80 ml (2.44 mmol, 1.25 eq) of 1.35 M *n*-butyllithium in hexane was then added in dropwise fashion, with vigorous stirring, over a period of 15 min while maintaining a temperature of -78° C. Stirring was continued for an additional 10 min to complete the formation of lithiomethyl propargyl ether. A solution of 446 mg (1.95 mmol) of aldehyde **17** in 10 ml of dry THF was then added dropwise with vigorous stirring, and after addition was complete the reaction was allowed to warm slowly to RT over the course of 1 h. The resulting solution was then quenched with 12 ml of 10% aqueous KH_2PO_4, and the aqueous layer was extracted with 3 x 10 ml of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Chromatography on silica gel then gave 509 mg (88%) of **36** as a pale yellow oil, Rf 0.34 (30% acetone/hexanes). Mass spectrum, m/e 297 (M^+); IR($CHCl_3$) 3315 cm^{-1}; NMR($CDCl_3$) δ 0.95 (d, 3H, J = 6 Hz), 1.31 (t, 3H, J = 7 Hz), 1.70 (m, 3H), 2.15 (s, 3H), 2.77 (m, 2H), 3.30 (s, 3H), 3.98 (q, 2H, J = 7 Hz), 4.08 (s, 2H), 4.49 (m, 1H).

2-(2-Methyl-4-oxo-7-methoxy-5-heptynyl)-4-methyl-5-ethoxythiazole (31b). This material was prepared from the acetylenic alcohol **36** in 85% yield following the general procedure of Swern *et al.*[13] The acetylenic ketone **31b** was isolated as a pale yellow oil, Rf 0.45 (30% acetone/hexanes). Mass spectrum, m/e 295 (M^+); IR($CHCl_3$) 2205, 1715, 1565 cm^{-1}; NMR($CDCl_3$) δ 1.01 (d, 3H, J = 6 Hz), 1.35 (t, 3H, J = 7 Hz), 2.20 (s, 3H), 2.57 (m, 3H), 2.76 (m, 2H), 3.39 (s, 3H), 4.02 (q, 2H, J = 7 Hz), 4.25 (s, 2H). **Anal.** Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74; S, 10.85. Found: C, 60.70; H, 7.40; N, 4.44; S, 10.60.

2-Ethoxy-3-methoxymethyl-4,5,6,7-tetrahydro-6-methylbenzo(*b*)thiophen-4-one (35b). A solution of 104 mg (0.35 mmol) of **31b** and 26 mg (0.07 mmol, 0.2 eq) of methylene blue in 20 ml of freshly distilled mesitylene was heated at reflux, with exclusion of light and air, for a period of 72 h. The mesitylene was then removed under reduced pressure to afford a dark oil. Chromatography on silica gel then gave 43 mg (48%, 62% based on recovered **31b**) of **35b** as a colorless oil, Rf 0.50 (30% acetone/hexanes). Mass spectrum, m/e 254 (M^+); IR($CHCl_3$) 1660, 1555, 1500 cm^{-1}; NMR($CDCl_3$) δ 1.14 (d, 3H, J = 6 Hz, collapsing to a singlet upon irradiation at 2.42, *6-Me*), 1.42 (t, 3H, J = 7 Hz, collapsing to a singlet upon irradiation at 4.13, $-OCH_2CH_3$), 2.30 (dd, 1H, J = 14, 12 Hz, collapsing to a doublet, J = 12 Hz, upon irradiation at 2.58, *H-7*), 2.42 (m, 1H, sharpens upon irradiation at 1.14, *H-6*), 2.58 (m, 2H, simplifies upon irradiation at either 2.30 or 2.95, *H-5'* and *H-7'*), 2.95 (dd, 1H, J = 15, 3 Hz, collapsing to a doublet, J = 3 Hz, upon irradiation at 2.58, *H-5*), 3.41 (s, 3H, $-CH_2OCH_3$), 4.13 (q, 2H, J = 7 Hz, collapsing to a singlet upon irradiation at 1.42, $-OCH_2CH_3$), 4.60 (s, 2H, $-CH_2OCH_3$). **Anal.** Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.60; H, 7.25.

3-Methyl-δ-valerothionolactone (40). A mixture of 3.26 g (28.7 mmol, 1.0 eq) of 3-methyl-δ-valerolactone and 6.6 g (16.3 mmol, 1.1 eq) of Lawesson's reagent in 40 ml of freshly distilled benzene was heated at reflux, under an atmosphere of nitrogen, for a period of 1.5 h.[22] The resulting yellow suspension was then cooled to RT, filtered through celite, and concentrated under reduced pressure to afford a yellow-orange gum. This residue was extracted with several portions of 8:2 hexane/CH_2Cl_2, and the combined extracts were filtered through silica gel to remove polar impurities.

Chromatography on silica gel, using hexane as eluant, then gave 2.4 g (64%) of **40** as a pale yellow oil, Rf 0.65 (CH_2Cl_2). IR(neat) 1260, 1235, 1150, 1080 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.07 (d, 3H, J = 5 Hz), 2.07 (m, 3H), 2.55 (dd, 1H, J = 18, 10 Hz), 3.26 (dd, 1H, J = 18, 6 Hz), 4.36 (m, 1H), 4.55 (m, 1H); ^{13}C NMR($CDCl_3$) 21 (-Me), 26 (-CH-), 30 (-CH_2-), 49 (-CH_2-), 71 (-OCH_2-), 222 (C=S). **Anal.** Calcd for $C_6H_{10}OS$: C, 55.36; H, 7.74. Found: C, 55.18; H, 7.70.

Thioamide 42. A mixture of 2.6 g (20 mmol, 1.0 eq) of thionolactone **40** and 500 mg (4.7 mmol, 0.24 eq) of anhydrous Na_2CO_3 in 50 ml of dry THF was cooled to 0° C, with vigorous stirring, and treated with 3.2 g (24 mmol, 1.2 eq) aminoacetaldehyde diethylacetal (**41**) in two portions. After stirring for 1 h at 0° C, the reaction mixture was filtered and concentrated under reduced pressure to afford a yellow oil. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 4.5 g (77%) of **42** as a pale yellow oil, Rf 0.48 (40% acetone/hexane). IR(neat) 1540 cm^{-1}; NMR($CDCl_3$) δ 0.98 (d, 3H, J = 7 Hz), 1.24 (2t, 6H, J = 7 Hz), 1.55 (m, 2H), 2.32 (m, 1H), 2.46 (br s, 1H, *-OH*), 2.54 (m, 1H), 2.74 (m, 1H), 3.6 (m, 2H), 3.7 (2q, 4H, J = 7 Hz), 3.82 (t, 2H, J = 5 Hz), 4.7 (t, 1H, J = 5 Hz), 8.4 (br, 1H, *-NH-*).

2-(2-Methyl-4-hydroxybutyl)-5-ethoxy-Δ-2-thiazoline (43). A solution of 1.6 g (6.08 mmol) of thioamide **42** in 10 ml of concentrated HCl was heated to 60° C for a period of 1 h. The reaction was then poured over 50 g of crushed ice, and the pH was adjusted to 8 with 10 N NaOH, followed by saturated Na_2CO_3. The aqueous layer was extracted with 3 x 50 ml of CH_2Cl_2, and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 0.97 g (74%) of **43** as a pale yellow oil, Rf 0.43 (40% acetone/hexane). IR(neat) 1730 (w), 1620 (m) cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 8 Hz), 1.20 (t, 3H, J = 8 Hz), 1.58 (m, 2H), 2.20 (m, 1H), 2.55 (m, 2H), 2.90 (br s, 1H, *-OH*), 3.38 (m, 1H), 3.57 (m, 1H), 3.65 (m, 2H), 4.10 (dd, 1H, J = 17, 7 Hz), 4.45 (d, 1H, J = 17 Hz), 5.59 (d, 1H, J = 7 Hz).

2-(2-Methyl-4-hydroxybutyl)thiazole (44). A solution of 3.5 g (16.1 mmol, 1.0 eq) of Δ-2-thiazoline **43** in 50 ml of freshly distilled toluene was treated with 1.7 g (17.7 mmol, 1.1 eq) of methanesulfonic acid, and the resulting mixture was heated at reflux for a period of 4 h. The toluene was then removed under reduced pressure and the residue was taken up in 150 ml of 1:1 H_2O/CH_2Cl_2. The pH of the aqueous phase was adjusted to 8 with 5% Na_2CO_3, and the aqueous layer was extracted with 3 x 75 ml of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 855 mg (31%) of **44** as a pale yellow oil, Rf 0.39 (40% acetone/hexane). IR(neat) 1740 (m), 1503 cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 8 Hz), 1.60 (m, 2H), 2.20 (m, 1H), 2.93 (dd, 1H, J = 16, 8 Hz), 3.07 (dd, 1H, J = 16, 6 Hz), 3.10 (br s, 1H, *-OH*), 3.72 (m, 2H), 7.20 (d, 1H, J = 2 Hz), 7.70 (d, 1H, J = 2 Hz). **Anal.** Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18; S, 18.72. Found: C, 56.07; H, 7.88; N, 8.01; S, 18.63.

2-(2-Methyl-4-oxobutyl)thiazole (45). This material was prepared from the thiazole alcohol **44** in 68% yield following the general procedure of Swern *et al.*[13] The aldehyde **45** was isolated as a pale yellow oil, Rf 0.61 (40% acetone/hexanes). IR(neat) 1725 cm^{-1}; NMR($CDCl_3$) δ 1.05 (d, 3H, J = 6 Hz), 2.36 (m, 1H), 2.56 (m, 2H), 3.00 (d, 2H, J = 6 Hz), 7.20 (d, 1H, J = 2 Hz), 7.70 (d, 1H, J = 2 Hz), 9.8 (s, 1H, *-CH=O*).

2-(2-Methyl-4-hydroxy-5-heptynyl)thiazole (46). This material was prepared from the thiazole aldehyde **45** in 73% yield following an identical procedure as that described for **34**. The acetylenic alcohol **46** was isolated as a pale yellow oil, Rf 0.49 (40% acetone/hexanes). IR(CH_2Cl_2) 2320 (w) cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 8 Hz), 1.70 (m, 2H), 1.84 (s, 3H), 2.30 (m, 1H), 2.92-3.15 (m, 2H), 4.45 (m, 1H), 7.20 (d, 1H, J = 2 Hz), 7.70 (d, 1H, J = 2 Hz). **Anal.** Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.78; H, 7.26; N, 6.34.

2-(2-Methyl-4-oxo-5-heptynyl)thiazole (37). This material was prepared from the acetylenic alcohol **46** in 87% yield following the general procedure of Swern *et al.*[13] The acetylenic ketone **37** was isolated as a pale yellow oil, Rf 0.61 (40% acetone/hexanes). IR(neat) 2220 (m), 1670 (s) cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 6 Hz), 2.04 (s, 3H), 2.45 (m, 1H), 2.65 (m, 2H), 3.00 (m, 2H), 7.22 (d, 1H, J = 2 Hz), 7.70 (d, 1H, J = 2 Hz). **Anal.** Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.34; N, 6.42.

4-(*p*-Toluenesulfonyl)-5-(2-methyl-4-hydroxybutyl)thiazole (49b). A solution of 2.55 g (13.08 mmol, 1.1 eq) of tosylmethylisocyanide (**47b**) in 75 ml of dry THF was cooled to -78° C in a flame dried flask under an atmosphere of nitrogen. A total of 5.2 ml (13.08 mmol, 1.1 eq) of 2.5 M *n*-butyllithium in hexane was then added in dropwise fashion, with vigorous stirring, over a period of 15 min to give a deep red solution. After stirring for an additional 30 min at -78° C, a solution of 1.55 g (11.89 mmol, 1.0 eq) of thionolactone **40** in 10 ml of dry THF was added dropwise while maintaining a temperature of -78° C. The resulting orange mixture was then stirred for 1 h at -78° C before quenching with 785 mg (13.08 mmol, 1.1 eq) of glacial acetic acid. After warming to 0° C, the reaction was poured into 100 ml of H_2O and extracted with 3 x 75 ml of CH_2Cl_2. The combined extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a dark oil. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 2.74 g (67%) of **49b** as a pale yellow oil, Rf 0.33 (40% acetone/hexane). IR(neat) 1700 (m) cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 6 Hz), 1.65 (m, 2H), 1.74 (s, 1H, *-OH*), 2.10 (m, 1H), 2.40 (s, 3H), 3.04 (dd, 1H, J = 14, 9 Hz), 3.50 (dd, 1H, J = 14, 5.5 Hz), 3.75 (m, 2H), 7.37 (d, 2H, J = 7.6Hz), 7.94 (d, 2H, J = 7.6Hz), 8.60 (s, 1H). **Anal.** Calcd for $C_{15}H_{19}NO_3S_2$: C, 55.36; H, 5.89; N, 4.30. Found: C, 55.51; H, 5.97; N, 4.25.

5-(2-Methyl-4-hydroxybutyl)thiazole (49a). *Method A.* A solution of 486 mg (11.8 mmol, 1.4 eq) of methylisocyanide (**47a**) in 30 ml of dry THF was cooled to -78° C in a flame dried flask under an atmosphere of nitrogen. A total of 5.5 ml (11.0 mmol, 1.3 eq) of 2.0 M *n*-butyllithium in hexane was then added in dropwise fashion, with vigorous stirring, over a period of 15 min to give a white suspension. After stirring for an additional 30 min at -78° C, the temperature was raised to -60° C. A solution of 1.10 g (8.46 mmol, 1.0 eq) of thionolactone **40** in 20 ml of dry THF was then added over a period of 30 min while maintaining a temperature of -60° C. The resulting yellow solution was then warmed to -40° C for 1 h and treated with 1.0 ml of HMPA. After an additional 2 h at -40° C, the resulting brown reaction mixture was quenched with 629 μl (1.4 eq) of glacial acetic acid. After warming to 0° C, the reaction was poured into 100 ml of H_2O and extracted with 3 x 50 ml of CH_2Cl_2. The combined extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a dark oil. Chromatography on silica gel, using 10% acetone/hexane as eluant, then gave 413 mg (28%) of **49a** as a pale yellow oil, Rf 0.37 (40% acetone/hexane), in addition to 528 mg (48%) recovered starting material **40**. IR(neat) 1731 (w) cm^{-1}; NMR($CDCl_3$) δ 0.88 (d, 3H, J = 6 Hz), 1.45 (m, 2H), 1.65 (m, 1H), 1.86 (m, 1H), 2.66 (dd, 1H, J = 14, 8 Hz), 2.80 (dd, 1H, J = 14, 6 Hz), 3.64 (m, 2H), 7.55 (s, 1H), 8.62 (s, 1H). **Anal.** Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18; S, 18.72. Found: C, 56.23; H, 7.67; N, 7.72 S, 18.55.

Method B. A mixture of 87 mg (3.6 mmol) of activated Mg in 10 ml of dry MeOH was heated to 50° C to initiate the generation of hydrogen.[28] A solution of 108 mg (0.33 mmol) of thiazole **49b** in 5 ml of dry MeOH was then added, and the resulting mixture was stirred at 40° C for 30 min before treating with a second 87 mg portion of Mg. After stirring for an additional 30 min at 40° C, followed by 1 h at RT, the reaction mixture was poured into 50 ml of cold, 50% saturated NH_4Cl, and the pH was adjusted to 7 with dilute HCl. Standard workup then afforded 34 mg (62%) of **49a**, identical in all respects with the material prepared by *method A* above.

5-(2-Methyl-4-oxobutyl)thiazole (50a). This material was prepared from the thiazole alcohol **49a** in 88% yield following the general procedure of Swern *et al.*[13] The aldehyde **50a** was isolated as a pale yellow oil, Rf 0.55 (40% acetone/hexane). IR(neat) 1725 cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 6 Hz), 2.20-2.60 (m, 3H), 2.90 (m, 2H), 7.60 (s, 1H), 8.70 (s, 1H), 9.78 (s, 1H, *CH=O*). **Anal.** Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55. Found: C, 57.05; H, 6.85.

4-(*p*-Toluenesulfonyl)-5-(2-methyl-4-oxobutyl)thiazole (50b). This material was prepared from the thiazole alcohol **49b** in 94% yield following the general procedure of Swern *et al.*[13] The aldehyde **50b** was isolated as a colorless solid, mp 77-78° C, Rf 0.52 (40% acetone/hexane). IR(CH_2Cl_2) 1725 cm^{-1}; NMR($CDCl_3$) δ 1.05 (d, 3H, J = 6 Hz), 2.40 (s, 3H), 2.55 (m, 3H), 3.35 (m, 2H), 7.34 (d, 2H, J = 7.6 Hz), 7.93 (d, 2H, J = 7.6 Hz), 8.63 (s, 1H), 9.80 (s, 1H, *CH=O*). **Anal.** Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.30; N, 4.33; S, 19.83. Found: C, 55.78; H, 5.41; N, 4.38; S, 19.87.

5-(2-Methyl-4-hydroxy-5-heptynyl)thiazole (51a). This material was prepared from the thiazole aldehyde **50a** in 75% yield following an identical procedure as that described for **34**. The acetylenic alcohol **51a** was isolated as a pale yellow oil, Rf 0.40 (40% acetone/hexanes) (diastereomeric mixture). IR(neat) 2240 cm^{-1}; NMR($CDCl_3$) δ 0.95 (2d, 3H), 1.40-1.80 (m, 2H), 1.90 (2s, 3H), 2.05 (m, 1H), 2.60-3.00 (m, 3H), 4.45 (m, 1H), 7.60 (s, 1H), 8.70 (s, 1H). **Anal.** Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.77; H, 7.32; N, 6.39.

4-(*p*-Toluenesulfonyl)-5-(2-methyl-4-hydroxy-5-heptynyl)thiazole (51b). This material was prepared from the thiazole aldehyde **50b** in 75% yield following an identical procedure as that described for **34**. The acetylenic alcohol **51b** was isolated as a pale yellow oil, Rf 0.40 (40% acetone/hexanes) (diastereomeric mixture). IR(CH_2Cl_2) 2220 cm^{-1}; NMR($CDCl_3$) δ 1.00 (2d, 3H), 1.60-1.90 (m, 2H), 1.85 (2s, 3H), 2.15 (m, 1H), 2.26 (2d, 1H, *-OH*), 2.43 (s, 3H), 3.09-3.50 (4 sets of dd, 2H), 4.50 (m, 1H), 7.34 (d, 2H, J = 7.6 Hz), 7.94 (d, 2H, J = 7.6 Hz), 8.62 (s, 1H). **Anal.** Calcd for $C_{18}H_{21}NO_3S_2$: C, 59.48; H, 5.82; N, 3.85; S, 17.64. Found: C, 59.65; H, 5.81; N, 3.71; S, 17.26.

5-(2-Methyl-4-oxo-5-heptynyl)thiazole (39). This material was prepared from the acetylenic alcohol **51a** in 77% yield following the general procedure of Swern *et al.*[13] The acetylenic ketone **39** was isolated as a pale yellow oil, Rf 0.51 (40% acetone/hexane). IR(neat) 2220, 1668 cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 7 Hz), 2.00 (s, 3H), 2.40 (m, 2H), 2.55 (m, 1H), 2.85 (m, 2H), 7.60 (s, 1H), 8.70 (s, 1H). **Anal.** Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.44; H, 6.37; N, 6.49.

4-(*p*-Toluenesulfonyl)-5-(2-methyl-4-oxo-5-heptynyl)thiazole (52). This material was prepared from the acetylenic alcohol **51b** in 85% yield following the general procedure of Swern *et al.*[13] The acetylenic ketone **52** was isolated as a colorless, crystalline solid, mp 132-133° C, Rf 0.54 (40% acetone/hexane). IR(CH_2Cl_2) 2230, 1675 cm^{-1}; NMR($CDCl_3$) δ 1.00 (d, 3H, J = 5 Hz), 2.00 (s, 3H), 2.40 (s, 3H), 2.45-2.70 (m, 3H), 3.33 (d, 2H, J = 5 Hz), 7.34 (d, 2H, J = 7.6 Hz), 7.94 (d, 2H, J = 7.6 Hz), 8.62 (s, 1H). **Anal.** Calcd for $C_{18}H_{19}NO_3S_2$: C, 59.81; H, 5.30; N, 3.87; S, 17.74. Found: C, 59.55; H, 5.31; N, 3.78; S, 17.76.

3,6-Dimethyl-4,5,6,7-tetrahydrobenzo(*b*)thiophene-4-one (38). *Method A. Thermolysis of 5-(2-methyl-4-oxo-5-heptynyl)thiazole (39).* A solution of 26.5 mg (0.12 mmol) of acetylenic thiazole **39** in 5 ml of freshly distilled, thoroughly degassed, benzene was heated at 240° C in the absence of light for 18 h (sealed tube). The solvent was then removed under reduced pressure and the residue purified by preparative TLC to afford 6.5 mg (30%) of **38** as a pale yellow oil, Rf 0.54 (20% acetone/hexane), in addition to 8.0 mg (30%) of recovered starting material **39**. IR(CH_2Cl_2) 1670 cm^{-1}; NMR($CDCl_3$) δ 1.14 (d, 3H, J = 7 Hz), 2.27 (m, 1H), 2.37 (d, 3H, J = 1.2 Hz, thiophene-*Me*), 2.50 (m, 2H), 2.60 (dd, 1H, J = 18, 12 Hz), 3.03 (dd, 1H, J = 18, 4 Hz), 6.65 (q, 1H, J = 1.2 Hz, thiophene-*H*). **Anal.** Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.65; H, 6.93.

Thiophene **38** was also obtained in 5% yield upon thermolysis of 2-(2-methyl-4-oxo-5-heptynyl)thiazole (**37**) (*Method B*), and in 5% yield upon thermolysis of 4-(*p*-Toluenesulfonyl)-5-(2-methyl-4-oxo-5-heptynyl)thiazole (**52**) (*Method C*).

3,6-Dimethyl-4,5,6,7-tetrahydrobenzo(*b*)thiophene-4-one, dithioethylene ketal (56). A solution of 17.0 mg (0.09 mmol, 1 eq) of thiophene ketone **38** in 10 ml of freshly distilled CH_2Cl_2 was treated with 13.3 mg (11.8 µl, 0.14 mmol, 1.5 eq) of 1,2-ethanedithiol and 0.76 mg (0.66 µl, 0.005 mmol, 0.05 eq) of BF_3-Et_2O at RT with vigorous stirring under an atmosphere of nitrogen. After stirring for 2 h, an additional 0.66 µl of BF_3-Et_2O was added and the reaction was kept overnight at RT. The resulting yellow solution was then quenched with 10 ml of 0.1 N NaOH, and the aqueous phase was extracted with 2 x 10 ml of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to afford a solid residue. Preparative TLC then gave 14.4 mg (63%) of **56** as a colorless, crystalline solid, mp 114-115° C, Rf 0.81 (10% acetone/hexane). IR(CH_2Cl_2) 1380 cm^{-1}; NMR($CDCl_3$) δ 1.10 (d, 3H, J = 7 Hz), 2.10 (m, 1H), 2.20 (m, 1H), 2.35 (m, 2H), 2.45 (s, 3H, thiophene-*Me*), 2.80 (m, 1H), 3.25 (m, 1H), 3.45 (m, 3H), 6.65 (s, 1H, thiophene-*H*).

α-Menthane (4α) and ß-Menthane (4ß). A solution of 4.0 mg (0.016 mmol) of dithiolane derivative **56** in 5 ml of hexane was treated with a suspension of 0.5 ml of freshly prepared W-7 Raney-nickel in 5 ml of absolute EtOH. The resulting mixture was heated at reflux for a total of 3 h, at which point TLC showed the complete disappearance of **56**. The Raney-nickel was then filtered and washed with 10 ml of hexane. The filtrate was diluted with 10 ml of H_2O, and the aqueous phase was extracted with 3 x 5 ml of hexane. The combined washings and extracts were then dried over anhydrous $MgSO_4$, filtered and concentrated to 5 ml. GC-MS analysis, standardized against authentic samples, showed 1% menthene **57**, 52% α-Menthane (**4α**), and 47% ß-Menthane (**4ß**) (99% total yield of menthanes). GC Column: 15 mm x 0.32 mm (ID), bound phase methyl silicone, 75° C isothermal, injection temperature = 250° C; Retention times: **4α** (3.65 min), **4ß** (4.02 min), **57** (3.80 min); MS:EI 70eV, **4α** and **4ß** : m/e 140; **57** m/e 138.

Thionolactone 63. A mixture of 507 mg (2.78 mmol, 1 eq) of lactone 62[18] and 591 mg (1.42 mmol, 1.02 eq) of Lawesson's reagent[22] in 3 ml of dry toluene was heated at reflux, under an atmosphere of nitrogen, for a period of 3.5 h. The resulting orange suspension was then cooled to RT and concentrated under reduced pressure to afford an orange gum. Chromatography on silica gel, using 5% acetone/hexanes as eluant, then gave 395 mg (78%) of **63** as a pale yellow, crystalline solid, mp 73-74° C (from hexanes), Rf 0.67 (20% acetone/hexanes). Mass spectrum, m/e 198 (M^+); IR(KBr) 1470, 1375, 1245, 1220 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.88 (d, 3H, J = 6.4 Hz), 0.93 (s, 3H), 1.20-1.91 (m, 8H), 3.07 (dd, 1H, J = 13.6, 2.2 Hz), 3.14 (dd, 1H, J = 13.6, 2.2 Hz), 3.89 (d, 1H, J = 11.4 Hz), 4.45 (d, 1H, J = 11.4 Hz). ^{13}C NMR($CDCl_3$) 30.51, 31.97, 35.20, 41.23, 44.27, 44.86, 49.59, 52.74, 58.96, 93.98, 238.57 (C=S). Anal. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.15; S, 16.17. Found: C, 66.70; H, 9.17; S, 16.11.

Thiazole alcohol 65b. A solution of 525 mg (2.69 mmol, 1.5 eq) of tosylmethylisocyanide (**47b**) in 11 ml of dry THF was cooled to -78° C in a flame dried flask under an atmosphere of nitrogen. A total of 1.02 ml (2.55 mmol, 1.43 eq) of 2.5 M *n*-butyllithium in hexane was then added in dropwise fashion, with vigorous stirring, over a period of 15 min to give an orange suspension. After stirring for an additional 10 min at -78° C, a solution of 354 mg (1.79 mmol, 1.0 eq) of thionolactone **63** in 6 ml of dry CH_2Cl_2 was added dropwise while maintaining a temperature of -78° C. The resulting clear orange solution was then warmed to -20° C and stirred for an additional 2.5 h before quenching with 146 μl (1.43 eq) of glacial acetic acid. The reaction was concentrated under reduced pressure to afford a brown residue, which was partitioned between 30 ml of CH_2Cl_2 and 25 ml of saturated $NaHCO_3$. The aqueous layer was extracted with 2 x 15 ml of CH_2Cl_2 and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to a light brown oil. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 551 mg (79%) of **65b** as a colorless, crystalline solid, mp 126-127° C (from ethyl acetate), Rf 0.28 (20% acetone/hexane). Mass spectrum, m/e 393 (M^+); IR(CH_2Cl_2) 3688, 3627, 3559, 1320, 1145 cm^{-1}; NMR($CDCl_3$) δ 0.83 (d, 3H, J = 6.8 Hz), 1.09 (s, 3H), 1.20-1.70 (m, 7H), 2.02 (m, 1H), 2.25 (m, 1H), 2.43 (s, 3H), 3.42 (dd, 1H, J = 15.0, 11.7 Hz), 3.49 (dd, 1H, J = 11.7, 3.9 Hz), 3.65 (br d, 1H, J = 12.0 Hz), 3.69 (d, 1H, J = 12.0 Hz), 7.34 (d, 2H, J = 8.5 Hz), 7.94 (d, 2H, J = 8.5 Hz), 8.60 (s, 1H). Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.04; H, 6.92; N, 3.45; S, 16.55. Found: C, 61.15; H, 6.96; N, 3.55; S, 16.47.

Thiazole alcohol 65a. *Method A.* A mixture of 6.7 g (16.8 mmol, 12 eq) of 6% sodium amalgam and 2.4 g (16.8 mmol, 12 eq) of Na_2HPO_4 in 14 ml of anhydrous MeOH was cooled to 0° C, with vigorous stirring, under an atmosphere of nitrogen. A solution of 551 mg (1.40 mmol) of **65b** in 14 ml of anhydrous THF was then added in one portion and vigorous stirring was continued. After 45 min, an additional 6 eq of both 6% sodium amalgam and Na_2HPO_4 were added simultaneously, and stirring was continued for 30 min. The reaction mixture was then poured into 30 ml of ice cold brine and extracted with 3 x 25 ml of CH_2Cl_2. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography on silica gel, using 20% acetone/hexanes as eluant, then gave 299 mg (89%) of **65a** as a colorless, crystalline solid, mp 107-108° C (from ethyl acetate), Rf 0.30 (20% acetone/hexanes). IR(CH_2Cl_2) 3621 cm^{-1}; NMR($CDCl_3$) δ 0.86 (d, 3H, J = 7.2 Hz), 1.23 (s, 3H), 1.20-1.60 (m, 6H), 1.70 (m, 2H), 1.83 (m, 1H), 2.91 (dd, 1H, J = 15.4, 11.6 Hz), 3.08 (dd, 1H, J = 15.4, 3.2 Hz), 3.65 (m, 2H), 7.58 (s, 1H), 8.67 (s, 1H). Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85; S, 13.39. Found: C, 65.24; H, 8.86; N, 5.84; S, 13.44.

Method B. Thiazole alcohol **65a** could also be derived in 25% yield by the reaction of lithiomethylisocyanide (**47a**) with the thionolactone **63**, using identical conditions as those reported for **49a** (*Method A*).

Thiazole aldehyde 66. This material was prepared from the thiazole alcohol **65a** in > 95% yield following the general procedure of Swern *et al.*[13] In a typical reaction, 229 mg of **65a** afforded 220 mg of aldehyde **66** as an unstable oil, Rf 0.33 (20% acetone/hexanes), which was used directly for the preparation of **67** without further purification. IR(CH_2Cl_2) 1718 cm^{-1}; NMR($CDCl_3$) δ 0.86 (d, 3H, J = 7.2 Hz), 1.08 (s, 3H), 1.20-1.64 (m, 6H), 1.79 (m, 1H), 2.09 (m, 1H), 2.86 (dd, 1H, J = 15.0, 4.0 Hz), 3.01 (dd, 1H, J = 15.0, 10.6 Hz), 7.54 (s, 1H), 8.63 (s, 1H), 9.59 (s, 1H).

Acetylenic alcohol 67. A solution of 385 mg (1.53 mmol, 1.3 eq) of triphenylmethane in 18 ml of dry THF was cooled to -78° C in a flame dried flask under an atmosphere of nitrogen. A total of 588 μl (1.53 mmol, 1.3 eq) of 2.60 M *n*-butyllithium in hexane was then added over a period of 5 min to afford a deep pink solution. Propyne gas was then passed over the solution until it was once again colorless. The lithiopropyne thus prepared was treated in a dropwise fashion with a solution of 271 mg (1.14 mmol, 1 eq) of thiazole aldehyde **66** in 9 ml of dry THF, and the resulting solution was stirred at -78° C for 3 h. The reaction was then quenched with 30 ml of 2.5% KH_2PO_4 and extracted with 3 x 20 ml of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography on silica gel, using 20% acetone/hexane as eluant, then gave 287 mg (91%) of **67** as a 55:45 diastereomeric mixture, Rf 0.31 (20% acetone/hexanes). Mass spectrum, m/e 277 (M^+); NMR($CDCl_3$) (major isomer) δ 0.86 (d, 3H, J = 6.6 Hz), 1.10 (s, 3H), 1.16-1.59 (m, 6H), 1.62 (m, 1H), 1.70-1.90 (m, 2H), 1.84 (d, 3H, J = 2.4 Hz), 2.94 (m, 1H), 3.52 (m, 1H), 4.45 (s, 1H), 7.56 (s, 1H), 8.66 (s, 1H).

Acetylenic ketone 58. This material was prepared from the acetylenic alcohol **67** in 93% yield following the general procedure of Swern *et al.*[13] In a typical reaction, 539 mg (1.94 mmol) of **67** afforded 495 mg of **58**. The acetylenic ketone **58** was isolated as a colorless, crystalline solid, mp 71-72° C (from ethyl acetate/hexanes), Rf 0.34 (20% acetone/hexane). Mass spectrum, m/e 275 (M^+); NMR($CDCl_3$) δ 0.81 (d, 3H, J = 7.2 Hz), 1.24 (s, 3H), 1.28-1.90 (br m, 7H), 1.96 (s, 3H), 2.15 (m, 1H), 2.64 (dd, 1H, J = 14.4, 3.2 Hz), 2.98 (dd, 1H, J = 14.4, 12.0 Hz), 7.52 (s, 1H), 8.62 (s, 1H). Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09; S, 11.64. Found: C, 69.84; H, 7.72; N, 5.07; S, 11.67.

Thiophene ketone 60. An appropriate reaction vessel was prepared by sealing one end of a 15 mm pyrex standard wall tube and constricting the other end 20 cm from the bottom. The tube was washed with saturated $NaHCO_3$, rinsed with distilled H_2O and absolute EtOH, thoroughly dried in an oven, and cooled in an inert atmosphere. A solution of 92 mg (0.33 mmol) of acetylenic ketone **58** in 10 ml of freshly distilled decalin was injected into the tube by means of a syringe equipped with a needle which was long enough to extend beyond the constriction. The tube was then attached to a vacuum manifold and subjected to five freeze-thaw cycles (liquid nitrogen, 0.002 mm). The degassed reaction mixture was then evacuated once again and sealed at the constriction with a flame. After warming to RT, the tube was placed in an oven maintained at 325° C and was heated for a period of 21 h. The resulting pale yellow reaction mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel to afford 67 mg (81%) of **60** as a colorless, amorphous solid, Rf 0.36 (2% ethyl acetate/hexanes). Mass spectrum, m/e 248 (M^+); IR(CH_2Cl_2) 1675 cm^{-1}; NMR($CDCl_3$) δ 0.83 (d, 3H, J = 7.0 Hz), 1.09 (s, 3H), 1.20-1.70 (m, 6H), 2.15 (m, 2H), 2.39 (d, 3H, J = 1.5 Hz, thiophene-*Me*), 2.90 (dd, 1H, J = 15.6, 5.6 Hz), 3.08 (dd, 1H, J = 15.6, 5.6 Hz), 6.60 (d, 1H, J = 1.5 Hz, thiophene-*H*). Exact mass. Calcd for $C_{15}H_{20}OS$: 248.1236. Found: 248.1232.

Thiophene 68. A solution of 820 µl (0.82 mmol, 2 eq) of 1 M $LiAlH_4$ in Et_2O was added in dropwise fashion, with stirring, to a solution of 219 mg (1.64 mmol, 4 eq) of $AlCl_3$ in 2 ml of anhydrous Et_2O under an atmosphere of nitrogen. The resulting solution was then treated with a solution of 102 mg (0.41 mmol, 1 eq) of thiophene ketone **60** in 3 ml of Et_2O, and stirring was continued for 1.5 h. The excess reagent was then destroyed by careful addition of 0.5 ml of ethyl acetate, and the reaction was poured into 10 ml of 20% H_2SO_4 and extracted with 2 x 5 ml of Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography on silica gel, using 1% ethyl acetate/hexanes as eluant, then gave 91 mg (94%) of **68** as a pale yellow oil, Rf 0.85 (2% ethyl acetate/hexanes). Mass spectrum, m/e 234 (M^+); IR(CH_2Cl_2) 1464, 1448, 1378, 1368 cm^{-1}; NMR($CDCl_3$) δ 0.89 (s, 3H), 0.92 (d, 3H, J = 3.0 Hz), 1.10-1.60 (m, 7H), 1.62-1.85 (m, 2H), 1.91 (d, 1H, J = 15.4 Hz), 2.05 (s, 3H, thiophene-*Me*), 2.52 (dd, 1H, J = 16.1, 4.0 Hz), 2.74 (dd, 1H, J = 15.4, 5.4 Hz), 6.66 (s, 1H, thiophene-*H*). **Exact mass.** Calcd for $C_{15}H_{22}S$: 234.1444. Found: 234.1445.

7-α-Eremophilane-6-one (61α). A solution of 90 mg of thiophene ketone **60** in 15 ml of hexanes was reacted with a 10-20 fold excess of freshly prepared W-7 Raney-nickel on a Parr hydrogenator in a 200 ml hydrogenation bottle. A heating mantle was used to maintain the external temperature at 90° C, with an internal pressure of 60 psi H_2. After 2 h the reaction was allowed to cool to RT and the catalyst was removed by gravity filtration. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by preparative TLC, to afford 72 mg (91%) of **61α** as a colorless oil, Rf 0.40 (2% ethyl acetate/hexanes), along with < 5% of the β-isomer **61β**. Mass spectrum, m/e 222 (M^+); IR(neat) 1701, 1461, 1454, 1385, 1370 cm^{-1}; NMR($CDCl_3$) δ 0.82 (d, 3H, J = 6.5 Hz), 0.84 (d, 3H, J = 7.8 Hz), 0.85 (d, 3H, J = 7.8 Hz), 1.13 (s, 3H), 1.20-1.62 (m, 8H), 1.78 (m, 2H), 1.90 (m, 1H), 2.08 (m, 1H), 2.31 (m, 1H), 2.41 (m, 1H). **Exact mass.** Calcd for $C_{15}H_{26}O$: 222.1985. Found: 222.1989.

7-β-Eremophilane-6-one (61β). A solution of 42 mg (0.19 mmol) of **61α** in 6 ml of anhydrous MeOH was treated with 1-2 mg of freshly prepared NaOMe, and the resulting solution was heated at reflux under an atmosphere of nitrogen for a period of 8 h. The reaction was then cooled to RT and concentrated under reduced pressure. The residue was taken up in 2 ml of CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 42 mg (100%) of **61β** as a colorless oil, Rf 0.40, 2% ethyl acetate/hexanes. The material thus obtained was homogeneous by TLC and contained < 2% **61α** by GC and NMR analysis. Mass spectrum, m/e 222 (M^+); IR(neat) 1701, 1461, 1451, 1381, 1364 cm^{-1}; NMR($CDCl_3$) δ 0.62 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 7.7 Hz), 0.90 (d, 3H, J = 7.7 Hz), 1.04 (s, 3H), 1.16-1.80 (m, 10H), 1.98-2.30 (m, 3H), 2.38 (m, 1H). **Exact mass.** Calcd for $C_{15}H_{26}O$: 222.1985. Found: 222.1980.

Eremophilane alcohol 69a. A solution of 25 mg (0.11 mmol) of 7-α-eremophilane-6-one (**61α**) in 1 ml of dry THF was added in a dropwise fashion, with vigorous stirring, to a solution of 220 µl (2 eq) of 1 M $LiAlH_4$/Et_2O in 1 ml of dry THF under an atmosphere of nitrogen. After stirring for 30 min at RT, excess $LiAlH_4$ was destroyed by adding 0.5 ml of ethyl acetate, and the reaction was poured into 5 ml of 10% H_2SO_4 and extracted with 3 x 5 ml of Et_2O. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Preparative TLC then afforded 21 mg (85%) of **69a** as a colorless oil, Rf 0.35 (2% ethyl acetate/hexanes). Mass spectrum, m/e 224 (M^+); IR(CH_2Cl_2) 3550, 3380, 1481, 1381, 1365 cm^{-1}; NMR($CDCl_3$) δ 0.71 (s, 3H), 0.90 (d, 3H, J = 6.4 Hz), 0.93 (d, 3H, J = 7.2 Hz), 0.94 (d, 3H, J = 7.2 Hz), 1.25-1.64 (m, 12H), 1.75 (m, 2H), 1.96 (m, 1H), 3.59 (d, 1H, J = 2.3 Hz). **Exact mass.** Calcd for $C_{15}H_{28}O$: 224.2144. Found: 224.2146.

Eremophilane alcohol 69b. This material was prepared from 7-β-eremophilane-6-one (**61β**) by an identical procedure as that described above for the isomeric alcohol **69a**. In a typical reaction, 25 mg of **61β** gave 19 mg (78%) of **69b** as a colorless oil, Rf 0.35 (2% ethyl acetate/hexanes). Mass spectrum, m/e 224 (M^+); IR(CH_2Cl_2) 3601, 1470, 1465, 1388, 1365 cm^{-1}; NMR($CDCl_3$) δ 0.80 (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 7.2 Hz), 0.96 (d, 3H, J = 7.2 Hz), 1.08 (s, 3H), 1.16-1.68 (m, 12H), 1.75 (m, 2H), 2.08 (m, 1H), 3.07 (d, 1H, J = 11.2 Hz). **Exact mass.** Calcd for $C_{15}H_{28}O$: 224.2144. Found: 224.2146.

Xanthate 70a. A solution of 36 mg (0.16 mmol) of eremophilane alcohol **69a** in 3 ml of dry THF was treated with a tenfold excess of NaH (60% oil dispersion) and 1 mg of imidazole. The resulting mixture was heated at reflux under an atmosphere of nitrogen for a period of 8 h. A tenfold excess of CS_2 was then added in a dropwise fashion, and heating was continued for an additional 30 min before quenching with a tenfold excess of CH_3I. After cooling to RT, a few drops of glacial acetic acid were added to destroy excess base, and the reaction was diluted with 10 ml of H_2O and extracted with 3 x 5 ml of CH_2Cl_2. The extracts were washed with dilute HCl, saturated $NaHCO_3$, and brine, before drying over anhydrous Na_2SO_4 and concentrating under reduced pressure. Preparative TLC then afforded 40 mg (79%) of **70a** as a colorless oil, Rf 0.65, 2% ethyl acetate/hexanes. Mass spectrum, m/e 314 (M^+); NMR($CDCl_3$) δ 0.87 (d, 3H, J = 9.1 Hz), 0.88 (d, 3H, J = 9.3 Hz), 0.98 (s, 3H), 0.99 (d, 3H, J = 8.2 Hz), 1.15-1.78 (m, 13H), 1.92 (m, 1H), 2.58 (s, 3H), 5.93 (br s, 1H). **Exact mass.** Calcd for $C_{17}H_{30}OS_2$: 314.1740. Found: 314.1738.

Xanthate 70b. This material was prepared from the eremophilane alcohol **69b** by an identical procedure as that described above for the isomeric xanthate **70a**. In a typical reaction, 22 mg of **69b** gave 24 mg (80%) of **70b** as a colorless oil, Rf 0.70 (2% ethyl acetate/hexanes). Mass spectrum, m/e 314 (M^+); IR(CH_2Cl_2) 1766, 1451, 1257, 1227 cm^{-1}; NMR($CDCl_3$) δ 0.78 (d, 3H, J = 8.2 Hz), 0.88 (d, 3H, J = 9.2 Hz), 0.94 (d, 3H, J = 9.2 Hz), 0.97 (s, 3H), 1.18-1.96 (m, 13H), 2.16 (m, 1H), 2.56 (s, 3H), 5.56 (d, 1H, J = 11.7 Hz). **Exact mass.** Calcd for $C_{17}H_{30}OS_2$: 314.1740. Found: 314.1738.

7-α-Eremophilane (5α). A solution of freshly distilled 18-crown-6 (10-fold excess) in 2 ml of anhydrous *t*-butylamine was stirred vigorously under an atmosphere of nitrogen and treated with an equivalent amount of oil-free potassium metal. After stirring for 30 min the characteristic royal blue color had appeared. A solution of 27 mg (0.086 mmol) of xanthate **70a** in dry THF was then added in a dropwise fashion, at such a rate as to maintain the blue color. After addition was complete, excess potassium was destroyed by the addition of EtOH, and the reaction mixture was partitioned between H_2O and Et_2O. The aqueous layer was extracted with 3 x 5 ml of Et_2O, and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Preparative TLC then gave 9 mg (50%, > 80% GC yield)[25] of **5α** as a colorless oil. Mass spectrum, m/e 208 (M^+); IR(neat) 1466, 1459, 1383, 1373 cm^{-1}; NMR($CDCl_3$) δ 0.84 (d, 6H, J = 6.5 Hz), 0.91 (s, 3H), 0.94 (d, 3H, J = 7.1 Hz), 1.11-1.82 (m, 16H). **Exact mass.** Calcd for $C_{15}H_{28}$: 208.2192. Found: 208.2191.

7-β-Eremophilane (5β). This material was prepared from the xanthate derivative 7β by an identical procedure as that described above for the isomeric 7-α-eremophilane (5α). In a typical reaction, 23 mg (0.074 mmol) of 7β afforded 7.5 mg (48%, > 80% GC yield)[25] of 5β as a colorless oil, which had identical IR and NMR spectra as an authentic sample.[26] Mass spectrum, m/e 208 (M^+); IR(neat) 1468, 1450, 1383, 1369 cm^{-1}; NMR($CDCl_3$) δ 0.70 (d, 3H, J = 6.8 Hz), 0.83 (s, 3H), 0.84 (d, 3H, J = 8.3 Hz), 0.842 (d, 3H, J = 8.3 Hz), 1.15-1.87 (m, 16H). Exact mass. Calcd for $C_{15}H_{28}$: 208.2192. Found: 208.2192.

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