Enynones in Organic Synthesis. 7. Substituent Effects on the α-Tocopherol-Catalyzed Cyclization of Enynones to Methylenecyclopentenones. Convenient Syntheses of Members of the Methylenomycin Class of Antibiotics

Peter A. Jacobi,* Harry L. Brielmann, and Reginald O. Cann

Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06459-0180

Received April 8, 1994®

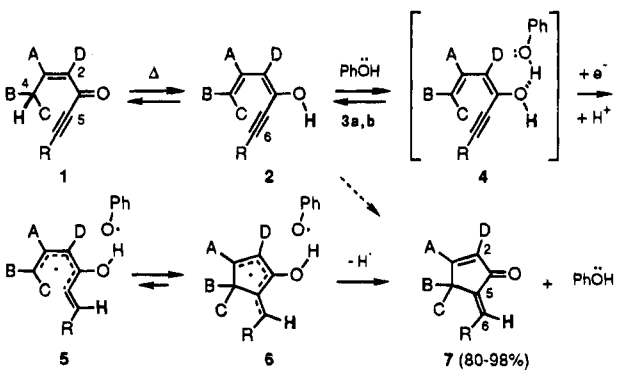
Substituent effects on the α-tocopherol (vitamin E, **3b**) catalyzed cyclization of a wide variety of enynones **1a–z** to methylenecyclopentenones **7a–z** have been examined, with particular emphasis given to electron-withdrawing and -donating groups at positions 2–4 and 6. In general, electron-withdrawing groups at positions 4 and 6 dramatically accelerate the cyclization process, while strong electron-donating groups at positions 3 and 4 completely inhibit reaction. Relatively little effect is exerted by groups at C-2, except for the methyl ester derivative **1i**, which is totally unreactive. This methodology was employed in the syntheses of the methylenecyclopentenone antibiotics methylenomycin B (**7a**) and desepoxy-4,5-didehydromethylenomycin A (**7z**) and in formal syntheses of methylenomycin A (**8**) and xanthocidin (**9**).

Introduction

In the preceding paper in this series we described a novel synthesis of methylenecyclopentenones of general structure **7** (D = H), which in favorable cases can be derived from enynones **1** via thermal isomerization to dienols **2**, followed by a symmetry-allowed (π^4s + σ^2s + π^2a) electrocyclic reaction (Scheme 1, dashed arrow).[1a] The efficiency of this transformation is highly dependent upon the nature of substituents A–C, being particularly enhanced by extended conjugation at C-4 (i.e., B,C = Ph or –CH=CH–; for consistency, enynone numbering corresponds to that of the derived 2-cyclopenten-1-ones). For less activated substrates (B,C = alkyl or H), the conversion **1** → **7** is very slow under thermal conditions, but it can be catalyzed by both thermal (SET) and photoassisted single electron transfer (PET).[2] In particular, phenols of low oxidation potential serve as efficient electron donors, with 4-*tert*-butylcatechol (**3a**) and α-tocopherol (vitamin E, **3b**) catalyzing the formation of **7** in yields of 80–98% (PET conditions). These results were rationalized by postulating a reversible single electron reduction via hydrogen-bonded species **4**, in which electron transfer occurs concomitant with intramolecular proton transfer from the enolic hydroxyl functionality to C-6 (bold **H**). Cyclization of the resultant vinylpentadienyl radical **5** to the highly stabilized ketylpentadienyl radical **6**, followed by hydrogen-atom abstraction, then completes the reaction sequence leading to **7**.

In view of the importance of the SET-catalyzed process, we have devoted considerable effort to studying substituent effects in transformations of the type summarized in Scheme 1. Previously we described the effect of alkyl and aryl substitution at C-3 and C-4 for the case where C-2 is unsubstituted.[1a,d] We have now expanded our studies to include a wide range of both electron-withdrawing and -donating substituents at (C-2)–(C-6). In addition, we have utilized this methodology for the syntheses of the important antibiotics methylenomycin B (**7a**) and desepoxy-4,5-didehydromethylenomycin A (**7z**)[1e] and in formal syntheses of methylenomycin A (**8**) and xanthocidin (**9**) (Figure 1).

Scheme 1



Discussion and Results

A. Synthesis of Methylenomycin B (7a) and Analogs. We initially explored the effect of substitution at C-2 (D) for the case where B,C = H and A = Me (Table 1, entries **1a–i**; for comparison, results from our earlier studies with **1A–E** [D = H] are included in italics). Enynones **1a–g** were readily prepared from the unsaturated aldehydes **11**, which in two cases were known in the literature (**11a,g**)[3a,b] and in others were easily derived from the corresponding esters **10c–f** (Scheme 2).[4a,b] Condensation of **11a–g** with the appropriate lithium

® Abstract published in *Advance ACS Abstracts*, August 1, 1994.

(1) (a) Jacobi, P. A.; Armacost, L. M.; Brielmann, H. L.; Cann, R. O.; Kravitz, J. I.; Martinelli, M. J. *J. Org. Chem.*, previous paper in this issue. Preliminary communications: (b) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865. (c) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J. *Tetrahedron Lett.* **1988**, *29*, 6869. (d) Jacobi, P. A.; Kravitz, J. I. *Tetrahedron Lett.* **1988**, *29*, 6873. (e) Jacobi, P. A.; Cann, R. O.; Skibbie, D. F. *Tetrahedron Lett.* **1992**, *33*, 2265.

(2) For leading references, see: (a) Mariano, P. S. *Acc. Chem. Res.* **1983**, *16*, 130. (b) Gassman, P. G.; Bottorff, K. J. *J. Am. Chem. Soc.* **1987**, *109*, 7547; *J. Org. Chem.* **1988**, *53*, 1097. (c) Lewis, F. D. *Acc. Chem. Res.* **1986**, *19*, 401.

(3) Aldehyde **11a**: (a) Brause, E. A.; Evans, E. A. *J. Chem. Soc.* **1955**, 3334. See also footnote 1e. Aldehyde **11g**: (b) Cutting, I.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1209.

(4) Esters **10c–e**: (a) Raap, R.; Chin, C. G.; Micetich, R. G. *Can. J. Chem.* **1971**, *49*, 2143. Ester **10f**: (b) Durman, J.; Grayson, J. I.; Hunt, P. G.; Warren. S. *J. Chem. Soc., Perkin Trans. I* **1986**, 1939.

0022-3263/94/1959-5305$04.50/0

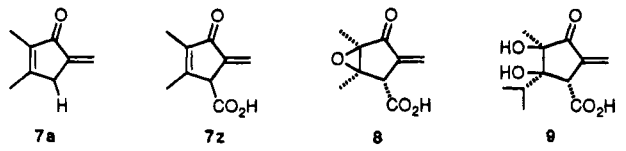
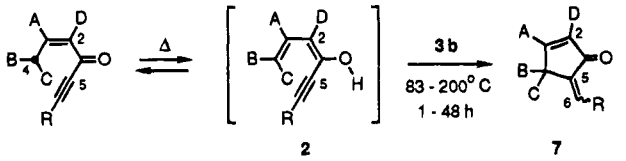


Figure 1.

Table 1

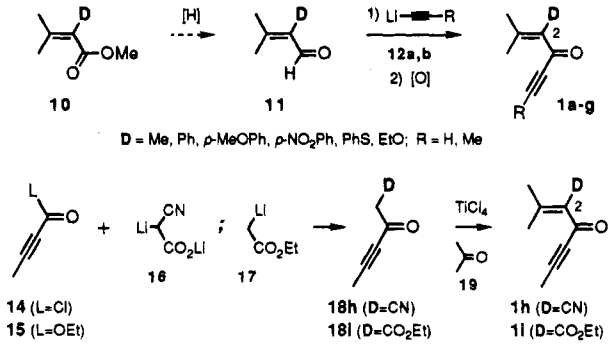


#	A	B	C	D	R	Rate[a]	%7[a]
1A	Me	H	H	H	Me	v. slow	13%
1B	Et	Me	H	H	Me	slow	56%
1C	Pr	Et	H	H	Me	slow	36%
1D	i-Pr	Me	Me	H	Me	med.	61%
1E	Bn	Ph	H	H	Me	v. fast	98%
1a	Me	H	H	Me	H	slow	55%
1b	Me	H	H	Me	Me	slow	52%
1c	Me	H	H	Ph	Me	med.	48%
1d	Me	H	H	p-MeOPh	Me	med.	46%
1e	Me	H	H	p-NO_2Ph	Me	fast (d.)[b]	30%
1f	Me	H	H	SPh	Me	slow	43%
1g	Me	H	H	OEt	Me	slow	36%
1h	Me	H	H	CN	Me	med. (d.)[b]	25%
1i	Me	H	H	CO_2Et	Me	NR	0%
1j	Me	H	H	Me	Ph	med.	30%
1k	Me	H	H	Me	p-MeOPh	fast	84%
1l	Me	H	H	Me	p-NO_2Ph	med.	24%
1m	Me	H	H	Me	SPh	fast	64%
1n	Me	H	H	Me	OMe	med. (d.)[b]	27%
1o	Me	H	H	Me	TMS	med.	45%
1p	Me	H	H	Me	CO_2Et	v. fast	87%
1q	Me	H	H	Me	CO_2t-Bu	v. fast	93%
1r	EtO	H	H	H	Me	NR	0%
1s	EtO	Et	H	H	Me	NR	0%
1t	$EtOCH_2$	EtO	H	Me	Me	isom.[c]	0%
1u	H	Et	H	H	Bu	isom.[d]	0%
1v	H	$CH_2O\Sigma$	H	H	Me	isom.[d]	0%
1w	i-Pr	$CH_2O\Sigma$	H	Me	H	v. fast	71%
1x	Me	$CH_2O\Sigma$	H	Me	H	v. fast	84%
1y	Me	CH_2OTHP	H	Me	H	v. fast	64%

(a) For more accurate comparison, all rates and yields are those for the thermal electron transfer process (SET). Generally higher yields were obtained under PET conditions. For R ≠ H, mixtures of (*E*)- and (*Z*)-isomers of **7** were usually obtained. (b) Low yield due to decomposition of starting material and/or product under reaction conditions. (c) Enynone **1t** undergoes exclusive isomerization to C-3 double bond isomer. (d) Enynones **1u,v** undergo exclusive isomerization to the corresponding (*E*)-isomer.

acetylides **12a,b** (**a**, R = H; **b**, R = Me) then afforded excellent yields of the expected acetylenic alcohols **13** (not shown), which upon oxidation with MnO_2 gave the desired enynones **1a–g** in straightforward fashion. Enynones **1h** and **1i** represented special cases, whose syntheses were modeled on the work of Townsend et al.[5a] and Wasserman et al.,[5b] respectively. Thus, reaction of acid chloride **14** with dilithium cyanoacetate (**16**) proceeded with spontaneous decarboxylation to afford acetylenic ketone **18h**,[5a] which upon $TiCl_4$-catalyzed condensation with acetone (**19**) gave **1h** in 88% yield.[6] In analogous fashion, acetylenic ketone **18i**, derived by Claisen condensation of ethyl tetrolate (**15**) with ethyl lithioacetate (**17**),[5b] afforded enynone **1i**, although in considerably lower yield (35%).

Scheme 2



Cyclization of **1a** to **7a** was of particular interest since this transformation would provide a convenient synthesis of methylenomycin B (**7a**) (Table 1).[7] Not surprisingly, **1a** was unreactive toward cyclization under purely thermal conditions, being recovered unchanged at temperatures up to 250 °C. This observation is in accord with our earlier experience with unactivated enynones[1a] and also with results described by Dreiding et al. employing the identical substrate **1a**.[8] These last authors obtained a 20% yield of **7a**, as part of a complex reaction mixture, upon thermolysis of **1a** at 610 °C in the gas phase.[8] In contrast to the uncatalyzed reaction, however, **1a** gave a 55% yield of **7a** upon heating at 200 °C/12 h with vitamin E (**3b**) under conditions of single electron transfer (SET) catalysis.[1e,7d] In identical fashion, enynone **1b** (R = Me) afforded 52% of the methylenomycin analog **7b**. The advantages to the SET-catalyzed process are thus clear (*note*: for more accurate comparison, relative rates and yields throughout are given for the thermal electron transfer process (SET), *even though the PET conditions were generally more efficient*).[1a]

As summarized in Table 1, both **1a** and **1b** underwent cyclization at a faster rate and in higher yield than model system **1A**, which is unsubstituted at C-2 (**1a,b** (12 h, 200 °C, ~55%) vs **1A** (48 h, 200 °C, 13%)). These results are in accord with the trend previously observed with enynones **1A–D**,[1a] in which alkyl substitution generally increases the rate of cyclization (cf. Table 1). In particular, isopropyl derivative **1D**, the only example where C = alkyl, and the most reactive of the simple *alkyl* substituted enynones **1**, afforded 61% of methylenecyclopentenone **7D** after 4 h at 200 °C. This reactivity pattern most likely reflects the relative stability of enols **2**, the key intermediates for cyclization to **7** (see also below).

Previously we found that *C-4* phenyl substituted enynone **1E** is much more reactive toward cyclization

(5) (a) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115. See also: Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. *Synthesis* **1984**, 1. (b) Wasserman, H. H.; Frechette, R.; Tatsuo, O.; van Duzer, J. H. *J. Org. Chem.* **1989**, *54*, 6012.

(6) Lange, J.; Kanabus-Kaminska, J. M.; Kral, A. *Synth. Commun.* **1980**, *10*, 473.

(7) For an extensive listing of references for the synthesis of **7a** prior to 1988, see: (a) Rizzo, C. J.; Dunlap, N. K.; Smith, A. B., III. *J. Org. Chem.* **1987**, *52*, 5280. For more recent studies, see: (b) Mathew, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1264. (c) Mikolajczyk, M.; Zatorski, A. *J. Org. Chem.* **1991**, *56*, 1217. (d) We are grateful to Professor Marc Tius, of the University of Hawaii, for providing us with an authentic sample of methylenomycin B (**7a**) and for NMR spectra of **44w**, **7y**, and **7z**: *cf.* refs 24a, 25a, and 26a, below.

(8) (a) Koller, M.; Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1986**, *27*, 19; (b) *Helv. Chim. Acta.* **1986**, *69*, 560 and references cited therein.

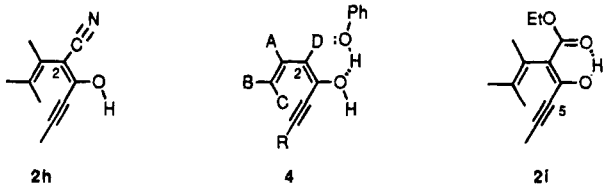
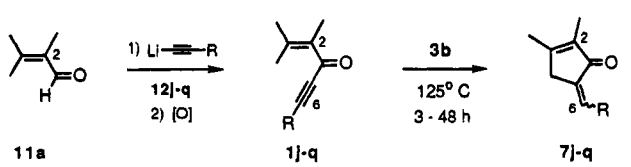


Figure 2.



than alkyl derivatives **1A–D** (Table 1).[1a,c] In part, this activation probably derives from a more favorable equilibrium between enynone **1E** and enol **2E**, since **2E** is stabilized by extended conjugation (note that **1E** will not be directly stabilized by a phenyl group at C-4). Also, electrochemical measurements, carried out on the corresponding enol acetates, indicate a substantial lowering of reduction potential in enol **2E** vs enols **2A–D**.[9] In contrast to the case with **1E**, however, *C-2* phenyl substituted enynones **1c–e** (D = Ph, *p*-MeOPh, *p*-NO_2-Ph) were only moderately more reactive as substrates than alkyl derivatives **1a,b** (D = Me) (Table 1). Thus, while **1E** gave a 98% yield of methylenecyclopentenone **7E** after 1 h at 125 °C, **1c–e** required 12–16 h at 200 °C to provide the corresponding cyclized products **7c–e** in yields of 30–50% (the low yield for **7e** appears to be due to decomposition under the reaction conditions). These results can be explained by the fact that both **1c–e** *and* **2c–e** will be stabilized by phenyl substituents at C-2. Therefore, the equilibrium between these species should not be appreciably different from the case with alkyl-substituted derivatives **1a,b** (vide supra). Finally, although not a pronounced effect, it did appear that *para* electron-withdrawing substituents had an accelerating influence on reaction rate (i.e. **1e** > **1c** ≈ **1d**), in agreement with an expected lowering of reduction potential in the corresponding enols **2**.[10] As predicted on the basis of this argument, electron-donating groups at C-2 had a mild retarding influence on cyclization (cf. **1f,g**).

The reactivity of enynones **1h** and **1i** was dramatically different. Not surprisingly (vide supra), **1h** (D = CN) cyclized to **7h** at a faster rate than the corresponding case with D = Me (**1b**), although yields were again lowered due to decomposition (cf. Table 1). In contrast, however, ester **1i** was completely unreactive toward cyclization to **7i**, even under the usually more efficient PET conditions. We believe that this last result is due to the fact that enol **2i** is strongly stabilized by an *intra*molecular hydrogen bond, which effectively prohibits the formation of activated complexes of type **4** (Figure 2; see also Scheme 1). Hydrogen bonding of the type found in **2i** is geometrically impossible with nitrile-substituted enol **2h**, which has otherwise similar electronic properties. As a consequence, cyclization of **2h** to **7h** occurs normally.[1e]

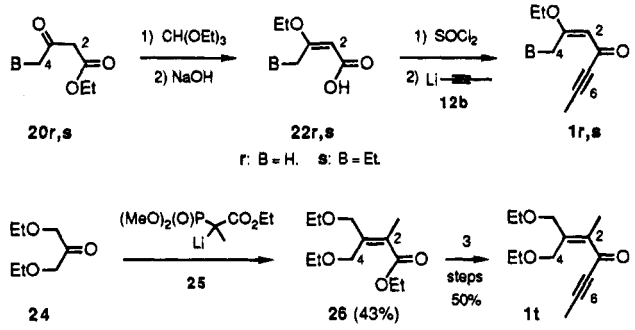
B. Substituent Effects at C-6, C-3, and C-4. 6-Substituted enynones **1j–q** were readily prepared by condensation of aldehyde **11a**[3a] with lithium acetylides **12j–q**,[11] followed by MnO_2 oxidation (Scheme 3; cf. also Scheme 2). Cyclization of **1j–q** to methylenecyclopentenones **7j–q** was then carried out using vitamin E (**3b**) as catalyst, and the rates were compared with enynones **1a,b** (R = H,Me), which have otherwise identical substituents (A,D = Me; B,C = H) (Table 1). In every case, reactivity of the 6-substituted analogs **1j–q** was enhanced. For example, enynone **1p** (R = CO_2Et) gave an 87% yield of cyclized product **7p** after 3.5 h at 125 °C (1,2-dichlorobutane), while **1a,b** (R = H,Me) required a temperature of 200 °C for reaction to proceed at a reasonable rate (~55% after 12 h). Similar results were obtained with enynone **1q** (R = CO_2-*t*-Bu), which afforded 93% of **7q** after 5 h at 125 °C. *It is important to note that neither* ***1p*** *nor* ***1q*** *underwent cyclization in the absence of catalyst* ***3b*** *or with poor electron donors such as p-nitrophenol (cf. ref 1a).* Interestingly, and in contrast to the case with 2-substituted enynones **1a–i**, electron-donating substituents at C-6 also had a rate-accelerating effect on cyclization to **7**. In some cases this effect was modest, as for example with **1n** (R = OMe), which gave a 27% yield of the unstable methylenecyclopentenone **7n** after 36 h at 125 °C. In other cases, however, acceleration was quite significant. Thus, **1m** (R = SPh) gave a 64% yield of **7m** after 9 h at 125 °C, which is considerably faster than cyclization of either **1a** (R = H) or **1b** (R = Me) (vide supra). Finally, an interesting trend was observed with aromatic substrates **1j–l** (R = Ph, *p*-MeOPh, *p*-NO_2Ph) in that reactivity increased with increasing electron-donating ability (i.e. **1k** > **1j** ≈ **1l**). Each of these cyclizations was carried out for 10 h at 125 °C to afford mixtures of methylenecyclopentenones **7j–l** plus unreacted enynones **1j–l**. Under these conditions, enynone **1k** (R = *p*-MeOPh) gave an 84% yield of cyclized product **7k** (15% recovered **1k**), while both **1j** and **1l** reacted only to the extent of 25–30% (70–75% recovered starting material; at 200 °C the yield of **1j** increased to 74%). This reactivity pattern is exactly the opposite of that observed above with 2-substituted enynones **1c–e** (i.e. **1e** > **1c** ≈ **1d**), and it might have mechanistic significance. However, at present we are unable to draw any firm conclusions.

(9) (a) Electrochemical measurements on enol acetates **2EAc** and **2BAc** were obtained with a three-electrode system using a PAR 174A polarographic analyzer coupled with an Allen 720E X-Y recorder.[9b] A platinum wire served as the working electrode and potentials were measured versus a 0.1 M $Ag/AgNO_3$ reference electrode. Measurements were made on 3.0 mM solutions of enol acetates in freshly distilled, degassed CH_2Cl_2 containing 0.125 M Et_4NPF_6. (b) We are grateful to Professor Albert J. Fry of this department for assistance with the electrochemical experiments and for many helpful discussions.

(10) (a) Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press: Cambridge, Great Britain, 1979. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, Ltd.: Chichester, Great Britain, 1985.

(11) Acetylenes **12j,o,p,u**: (a) Aldrich Chemical Co. Acetylene **12k**: (b) Allen, A. D.; Cook, C. D. *Can. J. Chem.* **1963**, *41*, 1084. See also: Al-Hassan, M. *J. Organomet. Chem.* **1990**, 227. Acetylene **12l**: (c) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. Acetylene **12m**: (d) Snider, B. B.; Kirk, T. C.; Roush, D. M.; Gonzales, D. *J. Org. Chem.* **1980**, *45*, 5015. Acetylene **12n**: (e) Wasserman, H. H.; Wharton, P. S. *J. Am. Chem. Soc.* **1960**, *82*, 661. Acetylene **12q**: (f) Sondheimer, F.; Stjernström, N.; Rosenthal, D. *J. Org. Chem.* **1959**, *24*, 1280.

Scheme 4



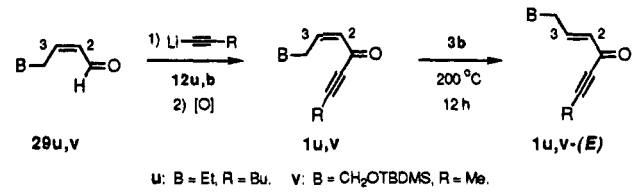
We next studied the effect of strongly electron donating groups at C-3 and C-4 (**1r–t**). Both **1r** (A = OEt, B = H) and **1s** (A = OEt, B = Et) were readily derived from the corresponding β-keto esters **20r,s**[12] by a four-step sequence involving initial conversion to the enol acids **22r,s**[13] followed by coupling of the derived acid chlorides **23r,s** (not shown) with 1-lithiopropyne (**12b**) (Scheme 4).[14,15] Enynone **1t** was prepared in a fashion analogous to that described above for 2-substituted isomers **1a–g** (cf. Scheme 2). Thus, Horner–Wadsworth–Emmons reaction of lithium trimethyl phosphonopropionate (**25**) with diethoxyacetone (**24**) gave a 43% yield of the expected ester derivative **26**,[16] which was conveniently converted to **1t** by a three-step sequence involving ester reduction to the corresponding aldehyde **27**, condensation with 1-lithiopropyne (**12b**), and oxidation of the resulting propargyl alcohol **28** (50% overall yield). Interestingly, substitution patterns of the type found in **1r–t** had a powerful inhibiting effect on enynone cyclization to **7** (cf. Table 1). Thus, both **1r** and **1s** were completely unreactive toward cyclization at temperatures up to 200 °C, returning only unreacted starting materials. These results were surprising in view of the fact that electron-donating groups at C-3 should increase the nucleophilicity at C-4 in enols **2** and thereby facilitate cyclization.[1a] Presumably this lack of reactivity reflects a higher LUMO energy in enols **2r,s** which precludes SET catalysis.[10] Enynone **1t** also gave no trace of the expected methylenecyclopentenone **7t** but instead suffered exclusive isomerization to the corresponding C-3 double-bond isomer (Table 1).

Finally, isomerization also dominated with enynones **1u,v**, which are unsubstituted at both C-2 and C-3 (Table 1). These materials were routinely available from the *(Z)*-aldehydes **29u,v**,[17,18] following an identical procedure as that utilized in the syntheses of **1j–q** (Scheme 5; cf. also Scheme 3). However, upon warming, both **1u** and **1v** underwent rapid isomerization to the corresponding *(E)*-isomers **1u,v-*(E)***, which proved to be completely unreactive toward cyclization to **7u,v**.

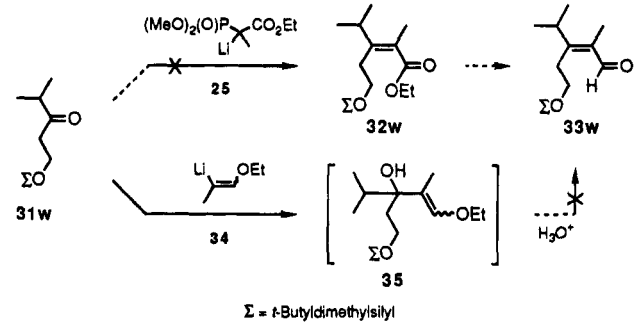
C. Synthesis of Desepoxy-4,5-didehydromethylenomycin A (7z) and Formal Syntheses of Methylenomycin A (8) and Xanthocidin (9). A key intermediate for our synthesis of xanthocidin (**9**) was the hydroxy aldehyde derivative **33w** (Σ = *tert*-butyldimethylsilyl), which we initially planned to prepare by a simple extension of the methodology used for the syntheses of enynones **1A–E** and **1t** (Scheme 6; cf. also Scheme 4).[1a] However, this approach turned out to be impractical. Thus, all attempts at Horner–Wadsworth–Emmons reaction of isopropyl ketone **31w** with lithium trimethyl phosphonopropionate (**25**) gave none of the desired ester **32w**,[16,19] most likely due to steric hindrance in **31w**. In an effort to circumvent this difficulty, we also explored the utility of lithiated enol ether **34**,[20a] which Boeckman et al. have elegantly employed as a 2-lithiopropionaldehyde equivalent.[20b] In the present case, **34** readily condensed with **31w** to give mixtures of tertiary alcohols **35**, which we expected might be directly converted to aldehyde **33w** by an acid-catalyzed Rupe rearrangement.[21] This last transformation worked quite well in model studies, albeit producing both *(E)*- and *(Z)*-enals. Unfortunately, however, all attempts at acid-catalyzed rearrangement of **35** afforded complex mixtures of products containing none of the desired **33w**.

We eventually found that **33w** could be prepared with complete control over double-bond geometry beginning

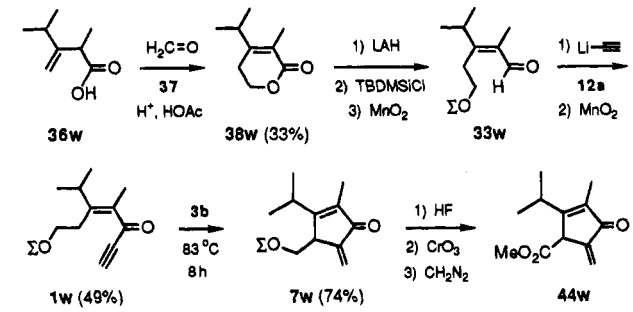
Scheme 5



Scheme 6



Scheme 7



(12) β-Keto esters **20r,s**: Aldrich Chemical Co.
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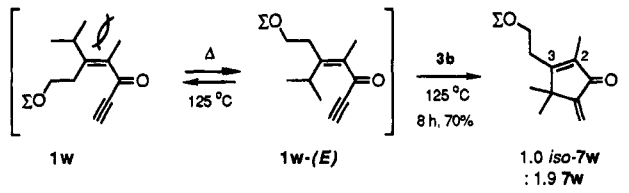


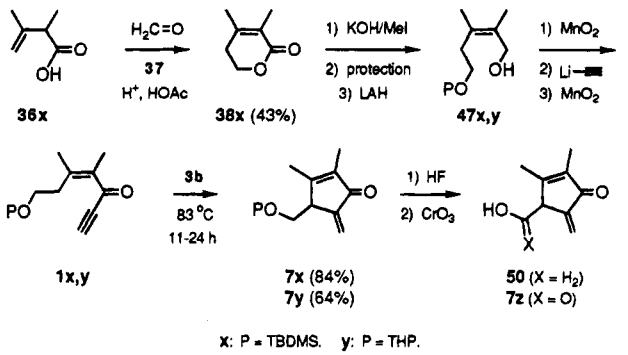
Figure 3.

with the carboxylic acid derivative **36w** (Scheme 7).[22] This route was based upon a novel synthesis of 5,6-dihydro-2-pyrones initially described by Nakagawa[23] and subsequently extended by Tamm.[18] Thus, Prins-like reaction of **36w** with formaldehyde (**37**) proceeded with spontaneous lactonization, affording a 33% yield of dihydropyrone **38w** which contained all of the functionality necessary for facile conversion to **33w**. The relatively modest yield for this transformation was more than compensated for by the simplicity of the experimental procedure and the fact that it was conveniently carried out on multigram scales. Dihydropyrone **38w** was then readily converted to **33w** by a straightforward sequence involving LAH reduction to the corresponding diol **39w** (not shown), selective protection of the least hindered hydroxyl group to give **40w** (TBDMSiCl), and MnO_2 oxidation. Finally, **33w** afforded a 49% overall yield of enynone **1w** upon condensation with lithioacetylene (**12a**) followed by oxidation (see also Scheme 2).

Once in hand, we were pleased to find that **1w** could be cleanly cyclized to methylenecyclopentenone **7w**, which was obtained in 74% yield after 8 h at 83 °C in the presence of **3b** (Scheme 7). Deprotection to afford alcohol **42w** (HF), followed by oxidation and esterification, then led in a staightforward fashion to methyl ester **44w** (75%), which has previously been converted to xanthocidin (**9**) by Tius et al.[7d,24 a] On the basis of these results, enynone **1w** is among the most reactive of the nonconjugated substrates examined thus far, presumably due to the inductive influence of the hydroxymethyl substituent at C-4. Interestingly, however, at higher temperatures **1w** exhibited a different reactivity pattern, in that *E,Z*-isomerization became a competing process (Figure 3; *note*: for convenience, the *Z*-isomer is defined as that isomer having the desired configuration for cyclization). Thus, at 125 °C enynone **1w** gave a 1.9:1.0 mixture of **7w** and *iso*-**7w** (70% yield), this last material being derived by cyclization of *E*-enynone **1w-*(E)***.

Our syntheses of desepoxy-4,5-didehydromethylenomycin A (**7z**) and methylenomycin A (**8**) followed much the same strategy as that described above for xanthocidin (**9**) (Scheme 8; see also Scheme 7). Thus, application of the Nakagawa methodology,[23] beginning with carboxylic acid **36x**,[22] provided a ready source of dihydropyrone **38x**, which was an ideal precursor for enynones **1x,y**. In this case, however, conversion of **38x** to the monoprotected diol **47x** was best accomplished by a three-step sequence involving initial cleavage to the corresponding methyl ester **45x** (KOH/MeI), followed by alcohol protection to give **46x** (TBDMSiCl), and LAH reduction (53% overall yield). All attempts at selective protection of the diol derived by direct reduction of **38x** failed (cf. Scheme 7). Once in hand, **47x** was readily transformed to the desired enynone **1x** by sequential MnO_2 oxidation to give aldehyde **48x** (93%), condensation with lithioacetylene (**12a**) (84%, **49x**), and reoxidation (55%). In analogous fashion, diol derivative **47y** (P = THP), prepared from **38x** by initial protection with dihydropyran (78%), was smoothly converted to enynone **1y** (P = THP).

Scheme 8



As in the case with enynone **1w** (Scheme 7), both **1x** and **1y** proved to be excellent substrates for electron-transfer-catalyzed cyclization. Thus, enynone **1y** gave a 64% yield of the known methylenecyclopentenone **7y** (P = THP) after 11 h at 83 °C in the presence of **3b** (Scheme 8).[7d,25 a] Since **7y** has previously been converted to methylenomycin A (**8**),[25a] this cyclization constitutes a formal synthesis of **8**. Finally, under identical conditions, **1x** gave an 84% yield of methylenecyclopentenone **7x** (P = TBDMS). This last material was then readily converted to desepoxy-4,5-didehydromethylenomycin A (**7z**) by deprotection to afford the known alcohol **50** (HF/MeCN; 92%), followed by oxidation according to the procedure of Tius et al. (CrO_3, 78%).[7d,26 a]

We believe that the methodology described in this paper could be utilized in the preparation of a wide range of natural products which contain either a cyclopentenone ring or a closely related functionality. This possibility is currently under investigation. In a following paper we describe a novel acid-catalyzed transformation of enynones of general structure **1** to give phenols, in particular members of the juncusol class of antimicrobial agents.[27]

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^1H NMR spectra were recorded at either 300 or 400 MHz and are expressed as ppm downfield from tetramethysilane.

3-Methyl-2-phenyl-2-butenal (11c). A suspension of 93.0 mg (2.50 mmol, 0.5 equiv) of lithium aluminum hydride (LAH) in 15.0 mL of Et_2O was cooled to −78 °C and treated in

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dropwise fashion, with vigorous stirring, with a solution of 1.00 g (4.90 mmol, 1.00 equiv) of ester **10c**[4a] in 10 mL of Et_2O. After addition was complete, the reaction mixture was allowed to warm slowly to rt and was stirred for an additional 2 h before excess LAH was destroyed by careful addition of a 1 M NaOH solution. The aqueous layer was then extracted with 3 × 20 mL of Et_2O and the combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 741 mg of the allylic alcohol corresponding to **11c**, which was utilized without further purification: R_f 0.30 (silica gel, CH_2Cl_2); MS *m/e* 162 (M^+); IR (neat) 3354, 3057, 2927, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 4.45 (s, 2H), 7.12–7.41 (m, 5H). The resulting crude allylic alcohol was taken up in 5 mL of CH_2Cl_2 and added in one portion to a stirring suspension of 6.36 g (74.1 mmol, 16.0 equiv) of MnO_2 in 60 mL of CH_2Cl_2 under a nitrogen atmosphere. Stirring was continued at rt for 24 h, and the reaction mixture was then filtered through Celite with thorough washing with CH_2Cl_2. The combined organic filtrates were concentrated under reduced pressure, and the product was purified by flash chromatograhy (silica gel, 10% EtOAc/hexanes) to give 716 mg (98%) of aldehyde **11c** as an unstable colorless oil: R_f 0.41 (CH_2Cl_2); MS *m/e* 160 (M^+); IR (neat) 3060, 2875, 1722, 1692, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.35 (s, 3H), 7.02 (d, J = 8.0 Hz, 2H), 7.28–7.40 (m, 3H), 10.25 (s, 1H).

2-(4-Methoxyphenyl)-3-methyl-2-butenal (11d). This material was prepared in 47% yield from ester **10d**[4a] following an analogous procedure to that described above for the preparation of aldehyde **11c**. **Intermediate allylic alcohol:** R_f 0.37 (silica gel, CH_2Cl_2); IR (neat) 3404, 2932, 1607, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.90 (s, 3H), 3.71 (s, 3H), 4.39 (s, 2H), 6.80 (d, J = 10.0 Hz, 2H), 7.11 (d, J = 10.0 Hz, 2H). **Aldehyde 11d** (unstable yellow oil): R_f 0.58 (silica gel, CH_2Cl_2); MS *m/e* 190 (M^+); IR (neat) 2952, 2838, 1712, 1677, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 3H), 2.32 (s, 3H), 3.70 (s, 3H), 6.88 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 10.24 (s, 1H).

3-Methyl-2-(4-nitrophenyl)-2-butenal (11e). This material was prepared in 58% yield from ester **10e**[4a] following an analogous procedure to that described above for the preparation of aldehyde **11c**. **Intermediate allylic alcohol:** R_f 0.26 (silica gel, 10% EtOAc/hexanes); MS *m/e* 189 ($M^+ - 18$ [H_2O]); IR (neat) 3345, 3060, 2925, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.96 (s, 3H), 4.45 (d, J = 4.80 Hz, 2H), 7.39 (d, J = 9.60 Hz, 2H), 8.20 (d, J = 9.60 Hz, 2H). **Aldehyde 11e** (unstable yellow oil): R_f 0.57 (silica gel, CH_2Cl_2); IR (neat) 2925, 2860, 1679, 1600, 1523, 1347, 1311, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.18 (s, 3H), 7.20 (d, J = 6.0 Hz, 2H), 8.22 (d, J = 6.0 Hz, 2H), 10.24 (s, 1H).

3-Oxo-4-hexynenitrile (18h). A solution of 1.72 g (20.2 mmol, 2.00 equiv) of freshly dried cyanoacetic acid and 5.0 mg (0.03 mmol) of dipyridyl in 125 mL of THF was cooled to −78 °C under nitrogen and was treated in a dropwise fashion, with vigorous stirring, with a solution of 16.1 mL (40.3 mmol, 4.00 equiv) of 2.50 M *n*-butyllithium/hexanes. After addition was complete, stirring was continued for 10 min at −78 °C, and the resulting pink solution of dianion **16** was then slowly treated with a solution of 1.03 g (10.1 mmol, 1.00 equiv) of 2-butynoyl chloride (**14**) in 15.0 mL of THF. The resulting light yellow reaction mixture was stirred at −78 °C for an additional 3 h, and the reaction was then quenched by pouring the solution into an ice-cold 4:1 mixture of Et_2O/1 M aqueous HCl. After warming to rt, the layers were separated and the aqueous phase was extracted with 3 × 30 mL of ether. The combined organic extracts were washed with 3 × 20 mL of saturated $NaHCO_3$, followed by 30 mL of saturated brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure, followed by rapid chromatography (silica gel, CH_2Cl_2) then afforded 0.58 g (54%) of keto nitrile **18h** as a highly unstable yellow oil which was utilized immediately for the preparation of **1h** (vide infra): R_f 0.62 (silica gel, 50% CH_2Cl_2/hexanes); MS *m/e* 107 (M^+); IR (neat) 2944, 2260, 2224, 1730, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.60 (s, 2H).

3-Oxo-4-hexynoic Acid, Ethyl Ester (18i). A solution of 6.30 mL (45.0 mmol, 2.20 equiv) of diisopropylamine in 80 mL of THF was cooled to 0 °C under nitrogen and was treated with 18.0 mL (45.0 mmol, 2.20 equiv) of 2.50 M *n*-butyllithium/hexanes. After stirring at 0 °C for 15 min, the resulting solution of lithium diisopropylamide was cooled to −78 °C and was then treated in a dropwise fashion with 4.40 mL (45.1 mmol, 2.21 equiv) of ethyl acetate (EtOAc). After addition was complete, stirring was continued at −78 °C for 1 h, and the resulting solution of enolate **17** was then cannulated into a solution of 2.00 g (20.4 mmol, 1.00 equiv) of ethyl 2-butynoate (**15**) in 10 mL of THF at −78 °C. The light yellow reaction mixture was stirred at −78 °C for 10 min and was then allowed to warm slowly to rt. After stirring for an additional 3 h at rt, the reaction mixture was diluted with 10 mL of saturated NH_4Cl, the layers were separated, and the aqueous phase was extracted with 2 × 50 mL of Et_2O. The combined organic extracts were washed with 2 × 50 mL of 1 M HCl, followed by 50 mL of 2% $NaHCO_3$, and were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was chromatographed (silica gel, 50% CH_2Cl_2/hexanes) to afford 1.86 g (70%) of a mixture of the keto ester **18i** and the corresponding enol as an unstable yellow oil which was utilized immediately for the preparation of **1i** (vide infra): R_f 0.67 (silica gel, 20% EtOAc/hexanes); MS *m/e* 154 (M^+); ^1H NMR (400 MHz, $CDCl_3$, keto–enol mixture) δ 1.26 (t, J = 7.2 Hz, 6H), 2.01 (s, 3H), 2.03 (s, 3H), 3.57 (s, 2H), 4.10 (q, J = 7.2 Hz, 4H), 5.25 (s, 1H), 11.9 (s, 1H).

Preparation of Enynones 1a–v: General Procedure. Method A. A solution of 0.10 mmol of triphenylmethane in 50.0 mL of THF was cooled to −78 °C under nitrogen and was treated with 6.89 mmol (2.80 equiv) of 2.5 M *n*-butyllithium/hexanes. The appropriate alkyne gas was then bubbled through the resulting pink solution until the color was discharged. After the mixture was stirred at −78 °C for an additional 15 min, a solution of 2.46 mmol (1.00 equiv) of the appropriate aldehyde in 5 mL of THF was added to the stirring colorless solution. After addition was complete, the reaction mixture was stirred at −78 °C for 1–4 h and was then quenched with 30 mL of brine. The layers were separated and the aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford an intermediate enynol. This last material was then directly converted to the corresponding enynone **1** by MnO_2 oxidation as previously described for the preparation of aldehyde **11c** above. **Method B.** A solution of 36.1 mmol (2.00 equiv) of the appropriate acetylene derivative **12** in 100 mL of THF was cooled to −78 °C under nitrogen and was treated with 34.7 mmol (1.92 equiv) of 2.50 M *n*-butyllithium/hexanes. The resulting solution of 1-lithioacetylide was stirred at −78 °C for 15 min and was then treated with a solution of 18.1 mmol (1.00 equiv) of the appropriate aldehyde in 25 mL of THF. After addition was complete, stirring was continued for 1–3 h and the reaction mixture was then allowed to slowly warm to rt. Workup and MnO_2 oxidation as described in method A above then afforded the desired enynone **1**. **Method C.** A solution of 61.2 mmol (2.00 equiv) of diisopropylamine in 100 mL of THF was cooled to 0 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 61.2 mmol (2.00 equiv) of 2.5 M *n*-butyllithium/hexanes. After stirring for 15 min at 0 °C, the resulting solution of lithium diisopropylamide was cooled to −78 °C and was treated slowly with 61.2 mmol (2.00 equiv) of the appropriate acetylene. The resulting solution of 1-lithioacetylide was stirred at −78 °C for 15 min and was then treated with a solution of 30.6 mmol (1.00 equiv) of the appropriate aldehyde in 25 mL of THF. After addition was complete, stirring was continued at −78 °C for 1 h and the reaction mixture was then allowed to slowly warm to rt. Stirring at rt was continued until TLC analysis indicated reaction was complete (generally overnight). Workup and MnO_2 oxidation as described in method A above then afforded the desired enynone **1**. **Method D.** A solution of 3.00 mmol (2.00 equiv) of 1 M $TiCl_4/CH_2Cl_2$ was slowly added to 9.5 mL of freshly distilled THF at 0 °C, forming a yellow precipitate. After addition was complete, stirrring was continued for 5 min

at 0 °C, and the yellow suspension was then slowly treated, with vigorous stirring, with a solution consisting of 1.50 mmol (1.00 equiv) of the appropriate 3-oxohexyne (**18h** or **18i**) and 3.54 mmol (2.37 equiv) of dry acetone in 2.0 mL of dry THF. The mixture turned brown immediately, and after 5 min of stirring, the reaction was slowly treated with a solution of 5.94 mmol of pyridine in 1.5 mL of THF at 0 °C. The resulting mixture was allowed to slowly warm to rt and stirring was continued overnight. At the end of this period, the solution was diluted with 25 mL of water, the layers were separated, and the aqueous layer was extracted with 3 × 25 mL of Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the crude product was chromatographed (silica gel) to give the desired enynones **1h** or **1i**. **Method E.** A solution of 0.10 mmol of triphenylmethane in 7.0 mL of THF was cooled to −78 °C under nitrogen and was treated with 11.4 mmol (1.00 equiv) of 2.5 M *n*-butyllithium/hexanes. Propyne gas was then bubbled through the resulting pink solution until the pink color was discharged. After the mixture was stirred at −78 °C for an additional 15 min, a solution of 11.4 mmol (1.00 equiv) of the appropriate acid chloride (**23r** or **23s**) in 20 mL of a solvent mixture consisting of 2:1:1 Et_2O:THF:petroleum ether was added to the solution, the cooling bath was removed, and the mixture was allowed to warm to rt. The reaction mixture was then poured into water and extracted with 4 × 25 mL of Et_2O. The combined ether extracts were dried (Na_2SO_4), evaporated *in vacuo*, and chromatographed to furnish enynones **1r** and **1s**.

4,5-Dimethyl-5-hexen-1-yn-3-one (1a). This material was prepared in 40% yield from aldehyde **11a**[3a] and acetylene **12a** following method A described above. **Intermediate acetylenic alcohol 13a** (colorless oil): R_f 0.70 (silica gel, 20% EtOAc/hexanes); MS *m/e* 124 (M^+); IR (CH_2Cl_2) 3589, 3448, 3295, 2990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.74 (s, 3H), 1.77 (s, 3H), 2.46 (s, 1H), 5.36 (br, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13, 20.5, 22.0, 62.0, 73, 84.3, 127, 130. **Enynone 1a**: R_f 0.31 (silica gel, 10% EtOAc/hexanes); MS *m/e* 121 ($M^+ - 1$ [H]); IR (CH_2Cl_2) 3005, 2921, 2873, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 1.98 (s, 3H), 2.14 (s, 3H), 3.27 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.4, 22.9, 23.8, 79.9, 82.9, 130, 149, 179; exact mass calcd for ($C_8H_{10}O$ + H) 123.0810, found 123.0819.

2,3-Dimethyl-2-hepten-5-yn-4-one (1b). This material was prepared in 80% yield from aldehyde **11a**[3a] and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13b** (yellow oil): R_f 0.70 (silica gel, 25% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.74 (s, 3H), 1.81 (s, 3H), 1.90 (s, 3H), 5.38 (s, 1H). **Enynone 1b** (light yellow oil): R_f 0.31 (silica gel, CH_2Cl_2); MS *m/e* 136 (M^+); IR (neat) 2920, 2233, 2025, 1648, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 4.12, 15.64, 22.88, 23.56, 81.51, 90.89, 130.44, 146.55, 181.21; exact mass calcd for $C_9H_{12}O$ 136.0888, found 136.0887.

2-Methyl-3-phenyl-2-hepten-5-yn-4-one (1c). This material was prepared in 51% yield from aldehyde **11c** and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13c** (yellow oil): R_f 0.69 (silica gel, CH_2Cl_2); MS *m/e* 200 (M^+); IR (neat) 3421, 2918, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 1.89 (s, 3H), 1.93 (s, 3H), 5.45 (s, 1H), 7.12−7.46 (m, 5H). **Enynone 1c** (light yellow oil): R_f 0.51 (silica gel, CH_2Cl_2); MS *m/e* 198 (M^+); IR (neat) 2919, 2211, 2202, 1649, 1605, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 3H), 1.80 (s, 3H), 2.21 (s, 3H), 7.15−7.40 (m, 5H); exact mass calcd for $C_{14}H_{14}O$ 198.1044, found 198.1043.

3-(4-Methoxyphenyl)-2-methyl-2-hepten-5-yn-4-one (1d). This material was prepared in 73% yield from aldehyde **11d** and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13d** (yellow oil): R_f 0.62 (silica gel, CH_2Cl_2); IR (neat) 3401, 2974, 2217, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.73 (s, 3H), 1.85 (s, 3H), 3.78 (s, 3H), 5.40 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H). **Enynone 1d** (yellow oil): R_f 0.81 (silica gel, CH_2Cl_2); MS *m/e* 228 (M^+); IR (neat) 2936, 2840, 2210, 1659, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.80 (s, 3H), 2.15 (s, 3H), 3.69 (s, 3H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H); exact mass calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1151.

2-Methyl-3-(4-nitrophenyl)-2-hepten-5-yn-4-one (1e). This material was prepared in 82% yield from aldehyde **11e** and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13e** (pale yellow oil): R_f 0.56 (silica gel, 2% MeOH/CH_2Cl_2); MS *m/e* 227 ($M^+ - 18$ [H_2O]); IR (neat) 3354, 2973, 2919, 2221, 1596, 1515 cm^{-1}. **Enynone 1e** (yellow oil): R_f 0.71 (silica gel, CH_2Cl_2); MS *m/e* 243 (M^+); IR (neat) 3104, 3075, 2918, 2852, 2233, 2210, 1644, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 1.82 (s, 3H), 2.28 (s, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 8.25 (d, *J* = 8.0 Hz, 2H); exact mass calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0892.

2-Methyl-3-(phenylthio)-2-hepten-5-yn-4-one (1f). This material was prepared in 22% yield by Pummerer rearrangement of the corresponding saturated sulfoxide:[4b] yellow oil; MS *m/e* 230 (M^+); IR (CH_2Cl_2) 2919, 2214, 1635, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 7.15−7.35 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 4.25, 23.4, 25.1, 81.3, 92.2, 126, 127, 129, 157, 178; exact mass calcd for $C_{14}H_{14}OS$ 230.0765, found 230.0774.

3-Ethoxy-2-methyl-2-hepten-5-yn-4-one (1g). This material was prepared in 46% yield from aldehyde **11g**[3b] and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13g** (yellow oil): R_f 0.27 (silica gel, 12% EtOAc/hexanes); MS *m/e* 150 ($M^+ - 18$ [H_2O]); ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.61 (s, 3H), 1.64 (s, 3H), 1.77 (s, 3H), 2.83 (br s, 1H), 3.83 (q, *J* = 7.0 Hz, 1H), 3.92 (q, *J* = 7.0 Hz, 1H), 5.1 (br, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 4.25, 16.0, 18.3, 18.9, 59.7, 69.4, 79.1, 80.9, 119, 147. **Enynone 1g** (pale yellow oil): R_f 0.41 (12% EtOAc/hexanes); MS *m/e* 166 (M^+); IR (CH_2Cl_2) 2980, 2916, 2864, 2222, 1733, 1651, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 8.0 Hz, 3H), 1.91 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 3.79 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 4.30, 15.3, 19.7, 20.3, 68.2, 80.9, 90.2, 138, 148, 177; exact mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1004.

2-(1-Methylethylidene)-3-oxo-4-hexynenitrile (1h). This material was prepared in 88% yield from 3-oxohexyne derivative **18h** following method D described above (unstable, low melting, pale yellow solid): R_f 0.65 (silica gel, CH_2Cl_2); MS *m/e* 146 ($M^+ - 1$ [H]); IR (CH_2Cl_2) 2959, 2927, 2856, 2251, 2227, 1652, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.34 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 4.69, 23.8, 28.3, 80.3, 94.9, 114, 117, 172, 174; exact mass calcd for (C_9H_9ON + H) 148.0724, found 148.0763.

2-(1-Methylethylidene)-3-oxo-4-hexynoic Acid, Ethyl Ester (1i). This material was prepared in 35% yield from 3-oxohexyne derivative **18i** following method D described above (pale yellow oil): R_f 0.57 (silica gel, 20% EtOAc/hexanes); MS *m/e* 194 (M^+); IR (CH_2Cl_2) 2984, 2223, 1723, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.5 Hz, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 4.25 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 3.80, 13.7, 22.5, 23.5, 60.7, 80.5, 91.1, 132, 155, 166, 176; exact mass calcd for ($C_{11}H_{14}O_3$ + H) 195.1022, found 195.1022.

4,5-Dimethyl-1-phenyl-4-hexen-1-yn-3-one (1j). This material was prepared in 66% yield from aldehyde **11a**[3a] and acetylene **12j**[11a] following method B described above. **Intermediate acetylenic alcohol 13j** (yellow oil): R_f 0.31 (silica gel, 10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 1.80 (s, 3H), 1.84 (s, 3H), 5.55 (s, 1H), 7.05−7.44 (m, 5H). **Enynone 1j** (yellow oil): R_f 0.77 (silica gel, CH_2Cl_2); MS *m/e* 197 ($M^+ - 1$ [H]); ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 7.33−7.59 (m, 5H); exact mass calcd for ($C_{14}H_{14}O$ − H) 197.0966, found 197.0966.

1-(4-Methoxyphenyl)-4,5-dimethyl-4-hexen-1-yn-3-one (1k). This material was prepared in 94% yield from aldehyde **11a**[3a] and acetylene **12k**[11b] following method B described above. **Intermediate acetylenic alcohol 13k** (yellow oil): R_f 0.20 (silica gel, 10% EtOAc/hexanes); IR (neat) 3452, 2936, 2839, 2188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.78 (s, 3H), 1.84 (s, 3H), 3.78 (s, 3H), 5.55 (s, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H).

Enynone 1k (yellow needles, mp 44–5 °C): R_f 0.57 (silica gel, 10% EtOAc/hexanes); IR (CCl_4) 3005, 2935, 2840, 2194, 1643, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.08 (s, 3H), 2.22 (s, 3H), 3.85 (s, 3H), 6.90 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.00; H 7.11.

4,5-Dimethyl-1-(4-nitrophenyl)-4-hexen-1-yn-3-one (1l). This material was prepared in 11% yield from aldehyde **11a**[3a] and acetylene **12l**[11c] following method B described above. **Intermediate acetylenic alcohol 13l** (yellow oil): R_f 0.16 (silica gel, 10% EtOAc/hexanes); IR (CCl_4) 3452, 2926, 2860, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.81 (s, 3H), 1.89 (s, 3H), 5.64 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H). **Enynone 1l** (dark yellow oil): R_f 0.41 (silica gel, 10% EtOAc/hexanes); MS m/e 242 (M^+ – 1 [H]); IR (CCl_4) 2925, 2202, 1643, 1587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.06 (s, 3H), 2.21 (s, 3H), 7.31 (d, J = 7.0 Hz, 2H), 8.25 (d, J = 7.0 Hz, 2H); exact mass calcd for ($C_{14}H_{13}NO_3$ – H) 242.0817, found 242.0819.

4,5-Dimethyl-1-(phenylthio)-4-hexen-1-yn-3-one (1m). This material was prepared in 84% yield from aldehyde **11a**[3a] and acetylene **12m**[11d] following method B described above. **Intermediate acetylenic alcohol 13m** (yellow oil): R_f 0.30 (silica gel, 10% EtOAc/hexanes); IR (neat) 3353, 2922, 2861, 2177, 1582, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 3H), 1.92 (s, 3H), 2.16 (s, 3H), 5.80 (s, 1H), 7.1–7.45 (m, 5H). **Enynone 1m** (bright yellow oil): R_f 0.85 (silica gel, 10% EtOAc/hexanes); MS m/e 230 (M^+); IR (neat) 3059, 2924, 2117, 1639, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.00 (s, 3H), 2.11 (s, 3H), 7.26–7.51 (m, 5H); exact mass calcd for $C_{14}H_{14}OS$ 230.0765, found 230.0763.

4,5-Dimethyl-1-methoxy-4-hexen-1-yn-3-one (1n). This material was prepared in 15% yield from aldehyde **11a**[3a] and acetylene **12n**[11e] following method C described above. **Intermediate acetylenic alcohol 13n** (yellow oil): MS m/e 136 (M^+ – 18 [H_2O]); ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 3.89 (s, 3H), 5.40 (d, J = 4.4 Hz, 1H). **Enynone 1n** (pale yellow oil): R_f 0.31 (silica gel, 10% EtOAc/hexanes); MS m/e 152 (M^+); IR (CH_2Cl_2) 2990, 2256, 1743, 1684, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 3H), 1.95 (s, 3H), 2.14 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.0, 22.7, 23.4, 44.2, 67.0, 104, 131, 144, 181; exact mass calcd for $C_9H_{12}O_2$ 152.0837, found 152.0843.

4,5-Dimethyl-1-(trimethylsilyl)-4-hexen-1-yn-3-one (1o). This material was prepared in 52% yield from aldehyde **11a**[3a] and acetylene **12o**[11a] following method C described above. **Intermediate acetylenic alcohol 13o** (yellow oil): R_f 0.33 (silica gel, 10% EtOAc/hexanes); MS m/e 178 (M^+ – 18 [H_2O]); ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.68 (s, 3H), 1.73 (s, 3H), 1.77 (s, 3H), 5.35 (s, 1H). **Enynone 1o** (pale yellow oil): R_f 0.80 (silica gel, 10% EtOAc/hexanes); MS m/e 193 (M^+ – 1 [H]); IR (CH_2Cl_2) 3010, 2961, 2867, 2150, 1711, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.88 (s, 3H), 1.99 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 0.00, 15.6, 23.0, 23.8, 98.6, 104, 130, 148, 180; exact mass calcd for $C_{11}H_{18}OSi$ 194.1127, found 194.1125.

5,6-Dimethyl-4-oxo-5-hepten-2-ynoic Acid, Ethyl Ester (1p). This material was prepared in 35% yield from aldehyde **11a**[3a] and acetylene **12p**[11a] following method C described above. **Intermediate acetylenic alcohol 13p** (light yellow oil): R_f 0.28 (silica gel, 10% EtOAc/hexanes); MS m/e 196 (M^+); IR (neat) 3403, 2983, 2928, 2230, 1713, 1591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 3H), 1.75 (s, 3H), 1.79 (s, 3H), 1.83 (s, 3H), 4.26 (q, J = 6.0 Hz, 2H), 5.49 (s, 1H). **Enynone 1p** (colorless oil): R_f 0.61 (silica gel, CH_2Cl_2); MS m/e 194 (M^+); IR (neat) 3308, 2956, 2871, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 5.0 Hz, 3H), 1.89 (s, 3H), 2.00 (s, 3H), 2.19 (s, 3H), 4.29 (q, J = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.4, 23.4, 24.4, 62.7, 79.8, 82.3, 129, 152.5, 153, 178; exact mass calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0944.

5,6-Dimethyl-4-oxo-5-hepten-2-ynoic Acid, *tert*-Butyl Ester (1q). This material was prepared in 30% yield from aldehyde **11a**[3a] and acetylene **12q**[11f] following method C described above. **Intermediate acetylenic alcohol 13p** (light yellow oil): R_f 0.31 (silica gel, 10% EtOAc/hexanes); IR (neat) 2982, 2245, 1714, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.87 (s, 3H), 1.96 (s, 3H), 2.24 (s, 3H), 5.26 (s, 1H). **Enynone 1q** (colorless oil): R_f 0.60 (silica gel, CH_2Cl_2); IR (neat) 2981, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.88 (s, 3H), 1.97 (s, 3H), 2.16 (s, 3H).

2-Ethoxy-2-hepten-5-yn-4-one (1r). This material was prepared in 5% yield from acid **22r**[13] and acetylene **12b** following method E described above (unstable yellow oil): R_f 0.65 (silica gel, 33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, J = 7.0 Hz, 3H), 1.91 (s, 3H), 2.25 (s, 3H), 3.83 (q, J = 7.0 Hz, 2H), 5.47 (s, 1H).

6-Ethoxy-5-nonen-2-yn-4-one (1s). This material was prepared in 38% yield from acid **22s**[13] and acetylene **12b** following method E described above (unstable yellow oil): R_f 0.48 (silica gel, 20% EtOAc/hexanes); MS m/e 180 (M^+); IR (neat) 2967, 1636, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.55 (m, 2H), 1.96 (s, 3H), 2.72 (t, J = 7.5 Hz, 2H), 3.83 (q, J = 7.0 Hz, 2H), 5.48 (s, 1H); exact mass calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1150.

1-Ethoxy-2-(ethoxymethyl)-3-methyl-2-hepten-5-yn-4-one (1t). This material was prepared in 60% yield from aldehyde **27** and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 28** (colorless oil): R_f 0.21 (silica gel, 10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–1.24 (m, 6H), 1.80 (s, 3H), 1.89 (s, 3H), 2.75 (br s, 1H), 3.36–3.49 (m, 4H), 5.28 (s, 1H). **Enynone 1t** (unstable yellow oil): R_f 0.41 (silica gel, 20% EtOAc/hexanes); IR (neat) 2979, 2932, 2218, 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 6H), 2.0 (br s, 6H), 3.45 (m, 4H), 4.10 (s, 2H), 4.20 (s, 2H).

(*Z*)-4-Dodecen-7-yn-6-one (1u). This material was prepared in 50% yield from aldehyde **29u**[17] and acetylene **12u**[11a] following method B described above. **Intermediate acetylenic alcohol 13u** (colorless oil; *Z*:*E* ratio = 2.50:1.00): R_f 0.45 (silica gel, 10% EtOAc/hexanes); MS m/e 165 (M^+ – 15 [CH_3]); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.96 (m, 6H), 1.35–1.54 (m, 6H), 1.77 (br s, 2H), 2.11 (dt, J = 3.8, 7.0 Hz, 2H), 5.13 (br, 1H), 5.5–5.62 (m, 2H). **Enynone 1u** (pale yellow oil): R_f 0.63 (silica gel, 3% EtOAc/hexanes); MS m/e 163 (M^+ – 15 [CH_3]); IR (CH_2Cl_2) 2932, 2875, 2213, 1674, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (q, J = 7.5 Hz, 6H), 1.41–1.61 (m, 6H), 2.37 (t, J = 7 Hz, 2H), 2.67 (q, J = 7 Hz, 2H), 6.13–6.26 (m, 2H).

(*Z*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-octen-6-yn-5-one (1v). This material was prepared in 41% yield from aldehyde **29v**[18] and acetylene **12b** following method A described above. **Intermediate acetylenic alcohol 13v** (colorless oil, *Z*:*E* ratio = 3:1): R_f 0.44 (silica gel, 20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.80 (s, 9H), 1.80 (s, 3H), 2.23–2.50 (m, 2H), 2.70 (br s, 1H), 3.52–3.70 (m, 2H), 5.08 (br d, 1H), 5.50–5.90 (m, 2H). **Enynone 1v** (pale yellow oil): R_f 0.60 (silica gel, 14% EtOAc/hexanes); ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 2.03 (s, 3H), 2.90 (q, J = 3.5 Hz, 2H), 3.73 (t, J = 3.5 Hz, 2H), 6.20 (d, J = 5.3 Hz, 1H), 6.35 (dt, J = 5.3, 3.5 Hz, 1H).

Preparation of 2-Cyclopenten-1-ones 7a–q: General Procedure. Method F. A solution of 0.36 mmol (1.00 equiv) of the appropriate enynone **1**, 0.39 mmol (1.10 equiv) of vitamin E, and 1.77 mmol (5.00 equiv) of 1,2-epoxyoctane (acid scavenger) in 3.00 mL of 1,2-dichlorohexane was transferred by dry syringe to a Pyrex tube which had previously been washed, rinsed with saturated $NaHCO_3$, followed by distilled H_2O, and dried at 150 °C overnight. The reaction mixture was degassed by freezing the tube under reduced pressure (0.25 mmHg) in a liquid nitrogen bath for 5 min, closing the stopcock, and then allowing the reaction mixture to warm to rt. The freeze–thaw process was repeated five times. The tube was then cooled under vacuum as before and sealed with an oxygen/propane gas torch. The sealed tube was allowed to warm to rt and was then heated in a preheated oven at 200 °C for 10–15 h. At the end of this period, the tube was carefully removed from the oven, allowed to cool to rt, frozen in a liquid nitrogen bath, and opened by touching a white-hot glass rod to an etched area of the tube. After the reaction mixture had warmed to rt, the solution was concentrated to dryness under reduced pressure, and the residue was chro-

matographed (silica gel) to afford the corresponding methylenecyclopentenone **7**. **Method G**. A solution of 0.36 mmol (1.00 equiv) of the appropriate enynone **1**, 0.38 mmol (1.10 equiv) of vitamin E, and 1.80 mmol (5.00 equiv) of 1,2-epoxyoctane (acid scavenger) in 6.0 mL of 1,2-dichlorobutane was degassed as described in method F and heated at reflux (124 °C) under a nitrogen atmosphere for 3–48 h. The solvent was removed by concentration under reduced pressure, and the residue was chromatographed (silica gel) to afford the corresponding methylenecyclopentenone **7**. **Method H**. A solution of 0.36 mmol (1.00 equiv) of the enynone **1**, 0.38 mmol (1.10 equiv) of vitamin E, and 1.80 mmol (5.00 equiv) of 1,2-epoxyoctane (acid scavenger) in 9.30 mL of 1,2-dichloroethane was degassed as described in method F and heated at reflux (84 °C) under a nitrogen atmosphere for 7–24 h. The solvent was removed by concentration under reduced pressure, and the residue was chromatographed (silica gel) to afford the corresponding methylenecyclopentenone **7**.

2,3-Dimethyl-5-methylene-2-cyclopenten-1-one (7a) [Methylenomycin B]. This material was prepared in 55% yield from enynone **1a** using method F described above (12 h). Purification by chromatography (silica gel, 100% CH_2Cl_2) afforded **7a** as a pale yellow oil, identical in all respects to an authentic sample:[7d] R_f 0.50 (silica gel, 10% EtOAc/hexanes); MS *m/e* 122 (M^+); IR (CH_2Cl_2) 3056, 2921, 2873, 1690, 1660, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.04 (s, 3H), 3.06 (br s, 2H), 5.30 (s, 1H), 6.01 (s, 1H); exact mass calcd for ($C_8H_{10}O$ + H) 123.1810, found 123.1900.

5-Ethylidene-2,3-dimethyl-2-cyclopentenone (7b). This material was prepared in 52% yield from enynone **1b** using method F described above (12 h, yellow oil, *Z:E* ratio = 1.4:1.0; 31% recovered **1b**). **(*Z*)-7b**: R_f 0.21 (silica gel, CH_2Cl_2); MS *m/e* 136 (M^+); IR (neat) 2926, 2857, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.05 (s, 3H), 2.28 (d, J = 7.00 Hz, 3H), 3.02 (s, 2H), 6.05 (q, J = 7.00 Hz, 1H). **(*E*)-7b**: R_f 0.10 (silica gel, CH_2Cl_2); MS *m/e* 136 (M^+); ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 3H), 1.82 (d, J = 7.00 Hz, 3H), 2,10 (s, 3H), 3.00 (s, 2H), 6.70 (q, J = 7.00 Hz, 1H).

5-Ethylidene-3-methyl-2-phenyl-2-cyclopentenone (7c). This material was prepared in 48% yield from enynone **1c** using method F described above (13 h, yellow oil, *E*-isomer only). **(*E*)-7c**: R_f 0.56 (silica gel, CH_2Cl_2); MS *m/e* 198 (M^+); IR (neat) 2928, 1694, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (d, J = 7.0 Hz, 3H), 2.22 (s, 3H), 3.20 (s, 2H), 6.70 (q, J = 7.0 Hz, 1H), 7.30–7.45 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 8.46, 16.8, 37.5, 129, 129, 129.8, 130, 130.3, 133, 136, 138, 163, 198; exact mass calcd for $C_{14}H_{14}O$ 198.1044, found 198.1043.

5-Ethylidene-2-(4-methoxyphenyl)-3-methyl-2-cyclopentenone (7d). This material was prepared in 46% yield from enynone **1d** using method F described above (13 h, yellow oil, *Z:E* ratio = 1.2:1.0). **(*Z*)-7d**: R_f 0.53 (silica gel, CH_2Cl_2); MS *m/e* 228 (M^+). **(*E*)-7d:** R_f 0.40 (silica gel, CH_2Cl_2); MS *m/e* 228 (M^+); IR (CCl_4) 2954, 2930, 1697, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (d, J = 7.2 Hz, 3H), 2.23 (s, 3H), 3.18 (s, 2H), 3.84 (s, 3H), 6.70 (q, J = 7.2 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 8.53, 16.5, 40.5, 55.3, 113, 128, 132, 132.9, 133, 135, 135.1, 140, 161, 161.2, 195; exact mass calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1151.

5-Ethylidene-3-methyl-2-(4-nitrophenyl)-2-cyclopentenone (7e). This material was prepared in 30% yield from enynone **1e** using method F described above (13 h, yellow oil, *E*-isomer only). **(*E*)-7e**: R_f 0.53 (silica gel, CH_2Cl_2); MS *m/e* 243 (M^+); IR (neat) 2927, 2859, 1697, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (d, J = 7.1 Hz, 3H), 2.24 (s, 3H), 3.23 (s, 2H), 6.73 (q, J = 7.1 Hz, 1H), 7.51 (d, J = 8.9 Hz, 2H), 8.25 (d, J = 8.9 Hz, 2H); exact mass calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0893.

3-Methyl-2-(phenylthio)-5-ethylidene-2-cyclopenten-1-one (7f). This material was prepared in 43% yield from enynone **1f** using method F described above (13 h, yellow oil, *Z:E* ratio = 1:1). **(*Z*)-7f**: R_f 0.35 (silica gel, 10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (d, J = 8.1 Hz, 3H), 2.27 (s, 3H), 3.27 (s, 2H), 6.17 (q, J = 8.1 Hz, 1H), 7.11–7.26 (m, 5H); **(*E*)-7f**: R_f 0.23 (silica gel, 10% EtOAc/hexanes); MS *m/e* 230 (M^+); IR ($CDCl_3$) 2962, 2926, 2856, 1692, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (d, J = 7.0 Hz, 3H), 2.11 (s, 3H), 3.31 (s, 2H), 6.85 (q, J = 7.0 Hz, 1H), 7.13–7.36 (m, 5H); exact mass calcd for $C_{14}H_{14}OS$ 230.0765, found 230.0772.

2-Ethoxy-3-methyl-5-ethylidene-2-cyclopenten-1-one (7g). This material was prepared in 36% yield from enynone **1g** using method F described above (13 h, yellow oil, *Z:E* ratio = 1:1). **(*Z*)-7g**: R_f 0.41 (silica gel, 10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.95 (d, J = 7.0 Hz, 3H), 2.05 (s, 3H), 2.93 (br s, 2H), 4.12 (q, J = 7.00 Hz, 2H), 6.06 (q, J = 6.80 Hz, 1H). **(*E*)-7g**: R_f 0.31 (silica gel, 10% EtOAc/hexanes); MS *m/e* 166 (M^+); IR ($CDCl_3$) 2919, 2861, 1690, 1661, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.0 Hz, 3H), 1.83 (d, J = 7.0 Hz, 3H,), 2.03 (s, 3H), 2.96 (br s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 6.68 (q, J = 7.1 Hz, 1H); exact mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

4-Ethylidene-2-methyl-5-oxo-1-cyclopentene-1-carbonitrile (7h). This material was prepared in 25% yield from enynone **1h** using method F described above (13 h, unstable yellow oil, *Z:E* ratio = 1:1). **(*Z*)-7h**: R_f 0.45 (silica gel, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.39 (d, J = 7.0 Hz, 3H), 3.31 (s, 2H), 6.28 (q, J = 7.0 Hz, 1H). **(*E*)-7h**: R_f 0.35 (silica gel, CH_2Cl_2); MS *m/e* 147 (M^+); ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.44 (d, J = 7.0 Hz, 3H), 3.32 (s, 2H), 6.81 (q, J = 7.0 Hz, 1H); exact mass calcd for (C_9H_9NO + H) 148.0724, found 148.0766.

5-(Phenylmethylene)-2,3-dimethyl-2-cyclopentenone (7j). This material was prepared in 30% yield from enynone **1j** using method F described above (12 h, yellow oil, *Z:E* ratio = 1.0:1.1). **(*Z*)-7j**: R_f 0.20 (silica gel, CH_2Cl_2); MS *m/e* 198 (M^+); ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.12 (s, 3H), 3.29 (s, 2H), 6.7 (s, 1H), 7.36–7.43 (m, 3H), 8.03 (d, J = 8.0 Hz, 2H). **(*E*)-7j**: R_f 0.10 (silica gel, CH_2Cl_2); MS *m/e* 198 (M^+); IR (neat) 2926, 1693, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.15 (s, 3H), 3.40 (s, 2H), 7.30–7.43 (m, 4H), 7.60 (d, J = 8.0 Hz, 2H); exact mass calcd for $C_{14}H_{14}O$ 198.1044, found 198.1043.

5-[(4-Methoxyphenyl)methylene]-2,3-dimethyl-2-cyclopentenone (7k). This material was prepared in 84% yield from enynone **1k** using method G described above (10 h, yellow oil, *Z:E* ratio = 1.7:1.0; 15% recovered **1k**). **(*E*)-7k**: R_f 0.20 (silica gel, 10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.16 (s, 3H), 3.38 (s, 2H), 3.88 (s, 3H), 6.92 (d, J = 6.0 Hz, 2H), 7.32 (s, 1H), 7.52 (d, J = 6.0 Hz, 2H). **(*Z*)-7k**: R_f 0.30 (silica gel, 10% EtOAc/hexanes); MS *m/e* 228 (M^+); IR (neat) 2935, 1692, 1629, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.09 (s, 3H), 3.21 (s, 2H), 3.85 (s, 3H), 6.68 (s, 1H), 6.90 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 8.5, 16.5, 40.5, 55.3, 113.3, 127.8, 131.4, 132.9, 133.0, 135.0, 135.1, 140.2, 160.5, 161.2, 195.0; exact mass calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1146.

2,3-Dimethy-5-[(4-nitrophenyl)methylene]-2-cyclopentenone (7l). This material was prepared in 24% yield from enynone **1l** using method G described above (10 h, orange needles, mp 142–44 °C from hexanes, *E*-isomer only; 75% recovered **1l**). **(*E*)-7l**: R_f 0.25 (silica gel, 20% EtOAc/hexanes); MS *m/e* 243 (M^+); IR (CCl_4) 2923, 1657, 1590, 1514, 1341, 1263, 1107, 1022, 926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.12 (s, 3H), 3.29 (s, 2H), 6.76 (s, 1H), 8.08 (d, J = 10.0 Hz, 2H), 8.20 (d, J = 10.0 Hz, 2H); exact mass calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0888.

2,3-Dimethyl-5-[(phenylthio)methylene]-2-cyclopentenone (7m). This material was prepared in 64% yield from enynone **1m** using method G described above (9 h, yellow oil, *E*-isomer only). **(*E*)-7m**: R_f 0.26 (silica gel, 10% EtOAc/hexanes); MS *m/e* 230 (M^+); IR (neat) 2921, 1665, 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.07 (s, 3H), 3.08 (s, 3H), 6.92 (s, 1H), 7.35–7.53 (m, 5H); exact mass calcd for $C_{14}H_{14}OS$ 230.0765, found 230.0765.

2,3-Dimethyl-5-(methoxymethylene)-2-cyclopenten-1-one (7n). This material was prepared in 27% yield from enynone **1n** using method G described above (10 h, yellow oil, *E*-isomer only). **(*E*)-7n**: R_f 0.25 (silica gel, 20% EtOAc/hexanes); MS *m/e* 152 (M^+); IR (CH_2Cl_2) 2851, 2763, 1698, 1661, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H),

2.05 (s, 3H), 3.02 (br s, 2H), 3.84 (s, 3H), 7.11 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.8, 21.2, 21.6, 44.0, 66.6, 104.2, 130.8, 144.0, 181.5; exact mass calcd for $C_9H_{12}O_2$ 152.0837, found 152.0841.

2,3-Dimethyl-5-[(trimethylsilyl)methylene]-2-cyclopenten-1-one (7o). This material was prepared in 45% yield from enynone **1o** using method G described above (48 h, yellow oil, *Z*:*E* ratio = 1:1). **(*Z*)-7o**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.77 (s, 3H), 2.05 (s, 3H), 3.04 (br s, 2H), 6.08 (s, 1H). **(*E*)-7o**: MS *m*/*e* 194 (M^+); IR (CH_2Cl_2) 2923, 2875, 1683, 1652, 1615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 9H), 1.79 (s, 3H), 2.10 (s, 3H), 3.07 (br s, 2H), 6.72 (s, 1H); exact mass calcd for $C_{11}H_{18}OSi$ 194.1127, found 194.1129.

2-(3,4-Dimethyl-2-oxo-3-cyclopenten-1-ylidene)acetic Acid, Ethyl Ester (7p). This material was prepared in 87% yield from enynone **1p** using method G described above (5 h, yellow oil, *Z*:*E* ratio = 1:1). **(*Z*)-7p**: R_f 0.30 (silica gel, 10% EtOAc/hexanes); MS *m*/*e* 194 (M^+); IR (neat) 2927, 2858, 1721, 1698, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 6.0 Hz, 3H), 1.78 (s, 3H), 2.10 (s, 3H), 3.10 (s, 2H), 4.32 (q, J = 6.0 Hz, 2H), 6.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.21, 14.3, 16.9, 37.2, 60.8, 118, 138, 148, 166.40, 167, 196. **(*E*)-7p**: R_f 0.21 (silica gel, 10% EtOAc/hexanes); MS 194 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 6.00 Hz, 3H), 1.80 (s, 3H), 2.18 (s, 3H), 3.48 (s, 2H), 4.25 (q, J = 6.00 Hz, 2H), 6.53 (s, 1H).

2-(3,4-Dimethyl-2-oxo-3-cyclopenten-1-ylidene)acetic Acid, *tert*-Butyl Ester (7q). This material was prepared in 93% yield from enynone **1q** using method G described above (5 h, yellow oil, *Z*:*E* ratio = 1.0:1.3). **(*Z*)-7q**: R_f 0.41 (silica gel, 10% EtOAc/hexanes); MS *m*/*e* 222 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 1.78 (s, 3H), 2.05 (s, 3H), 3.08 (s, 2H), 5.99 (s, 1H). **(*E*)-7q**: R_f 0.26 (silica gel, 10% EtOAc/hexanes); MS *m*/*e* 222 (M^+); IR (neat) 2928, 1722, 1697, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.76 (s, 3H), 2.11 (s, 3H), 3.40 (s, 2H), 6.40 (s, 1H); exact mass calcd for $C_{13}H_{18}O_3$ 222.1255, found 222.1256.

4-Ethoxy-3-(ethoxymethyl)-2-butenoic Acid, Ethyl Ester (26). A solution of 6.20 g (0.03 mol) of triethyl 2-phosphonopropionate in 75 mL of dry THF was cooled to −78 °C under nitrogen and was treated with 10.5 mL (0.03 mmol, 1.00 equiv) of a 2.5 M solution of *n*-butyllithium/hexanes. After the solution was stirred for 15 min at −78 °C, a total of 3.00 g (0.03 mmol, 1.00 equiv) of 1,1-diethoxy-2-propanone was added in portions. The reaction mixture was then allowed to warm slowly to rt, and after the mixture was stirred a total of 14 h, the reaction was quenched with 50 mL of saturated brine. The aqueous phase was extracted with Et_2O, and the combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a tan oil. Chromatography (silica gel, 10% EtOAc/hexanes) then gave 2.58 g (43%) of ester **26** as a light yellow, unstable oil: R_f 0.55 (silica gel, 10% EtOAc/hexanes); IR (neat) 2976, 2869, 1722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 8.0 Hz, 3H), 1.21 (t, J = 8.0 Hz, 3H), 1.30 (t, J = 8.0 Hz, 3h), 1.96 (s, 3H), 3.45 (q, J = 8.0 Hz, 2H), 3.49 (q, J = 8.0 Hz, 2H), 4.10 (s, 2H), 4.19 (s, 2H), 4.21 (q, J = 8.0 Hz, 2H).

4-Ethoxy-3-(ethoxymethyl)-2-methyl-2-butenal (27). This material was prepared in 37% yield from ester **26** following the general procedure described above for aldehyde **11c**. **Intermediate allylic alcohol:** R_f 0.46 (silica gel, 10% EtOAc/hexanes); IR (neat) 3425, 2974, 2873, 1676, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (m, 6H), 1.90 (s, 3H), 2.25 (s, 1H), 3.41−3.58 (m, 4H), 4.02 (s, 2H), 4.12 (s, 2H). **Aldehyde 27** (unstable yellow oil): R_f 0.60 (silica gel, 20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (m, 6H), 1.86 (s, 3H), 3.52−3.60 (m, 4H), 4.26 (s, 2H), 4.46 (s, 2H), 10.23 (s, 1H).

2,4-Dimethyl-3-methylenepentanoic Acid (36w). This material was prepared in 97% yield from 4-methyl-3-methylenepentanoic acid following the general procedure of Van Karpf:[22a] colorless oil, MS *m*/*e* 142 (M^+); IR (CH_2Cl_2) 3499, 3194, 2875, 1745, 1705, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H), 1.33 (d, J = 6.0 Hz, 3H), 2.31−2.42 (m, 1H), 3.17 (q, J = 6.0 Hz, 1H), 4.99 (br s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.6, 22.2, 22.4, 34.3, 44.0, 109, 157, 182.

5,6-Dihydro-2-methyl-3-(1-methylethyl)-2*H*-pyran-2-one (38w).[23] A mixture of 4.36 g (30.7 mmol) of acid **36w**, 33.7 mmol (1.00 equiv) of paraformaldehyde (**37**), 7.84 mL of acetic acid, and 0.20 mL of concd H_2SO_4 was heated at 105 °C (oil bath) for 8 h . At the end of this period, the reaction mixture was cooled to rt and treated with 1.00 g of anhydrous NaOAc, and most of the acetic acid was removed under reduced pressure followed by concentration from 50 mL of benzene. The residue was dissolved in 100 mL of Et_2O, which was washed sequentially with 20 mL of H_2O and 20 mL of saturated brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure followed by chromatography (silica gel, 20% EtOAc/hexanes) then afforded 1.55 g (33%) of **38w** as a pale yellow oil: R_f 0.52 (20% EtOAc/hexanes); MS *m*/*e* 154 (M^+); IR (CH_2Cl_2) 2931, 2900, 2876, 1704, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 6H), 1.90 (s, 3H), 2.33 (t, J = 7.0 Hz, 2H), 2.92−3.04 (m, 1H), 4.26 (t, J = 7.0 Hz, 2H); exact mass calcd for ($C_9H_{14}O_2$ + H) 155.1072, found 155.1072.

(*Z*)-2-Methyl-3-(1-methylethyl)-2-pentene-1,5-diol (39w). A suspension of 0.29 g (7.16 mmol, 1.20 equiv) of lithium aluminum hydride (LAH) in 200 mL of dry THF was cooled to 0 °C and treated in dropwise fashion, with vigorous stirring, with a solution of 0.92 g (5.97 mmol, 1.00 equiv) of lactone **38w** in 10.0 mL of THF. After addition was complete, the reaction mixture was allowed to warm slowly to rt and was stirred for an additional 1 h before the reaction was quenched with 11.5 mL of 10% aqueous NaOH. The resulting suspension was filtered through Celite and the residue was washed several times with Et_2O. The combined organic filtrates were concentrated under reduced pressure and the crude product was chromatographed (silica gel, 30% acetone/hexanes) to yield 0.65 g (70%) of 1,5-diol **39w** as a colorless viscous oil: R_f 0.11 (30% EtOAc/hexanes); MS *m*/*e* 158 (M^+); IR (CH_2Cl_2) 3612, 3450, 2875, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.4 Hz, 6H), 1.80 (s, 3H), 2.38 (t, J = 6.4 Hz, 2H), 2.78−2.87 (m, 1H), 3.60 (t, J = 6.4 Hz, 2H), 4.02 (s, 2H).

(*Z*)-2-Methyl-3-(1-methylethyl)-5-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2-penten-1-al (33w). A solution of 0.60 g (3.80 mmol, 1.00 equiv) of diol **39w** in 48 mL of CH_2Cl_2 was cooled to 0 °C and treated sequentially with 0.64 mL (4.59 mmol) of Et_3N, 0.63 g (4.18 mmol, 1.10 equiv) of *tert*-butyldimethylsilyl chloride (TBDMSiCl), and 19 mg (0.15 mmol, 0.04 equiv) of (*N*,*N*-dimethylamino)pyridine (DMAP). After addition was complete, the reaction mixture was allowed to warm to rt and stirring was continued for 41 h. At the end of this period, the reaction was diluted with 170 mL of ether, the precipitate was separated, and the filtrate was washed with 3 × 30 mL of 10% aqueous HCl and 20 mL of saturated brine. The organic layers were then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed, (silica gel, 10% EtOAc, hexanes) to give 0.59 g of an inseparable 2.4:1.0 mixture of **40w** and the isomeric alcohol 2,3-dimethyl-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-buten-5-ol (colorless oil): R_f 0.32 (silica gel, 12% EtOAc/hexanes); MS *m*/*e* 229 (M^+ − 43 [C_3H_7]). MnO_2 oxidation of this mixture as previously described for aldehydes **11c−e**, followed by chromatography, then gave 0.20 g (30%) of **33w** as a colorless unstable oil: R_f 0.68 (10% EtOAc/hexanes); MS *m*/*e* 269 (M^+ − 1 [H]); IR (CH_2Cl_2) 2930, 2885, 2858, 1729, 1682, 1663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.08 (d, J = 9.3 Hz, 6H), 1.77 (s, 3H), 2.74 (t, J = 9.3 Hz, 2H), 3.00−3.11 (m, 1H), 3.68 (t, J = 9.3 Hz, 2H), 10.07 (s, 1H).

(*Z*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methyl-3-(1-methylethyl)-3-hepten-6-yn-5-one (1w). This material was prepared in 49% yield from aldehyde **33w** and acetylene **12a** following method A described above. **Intermediate acetylenic alcohol 41** (colorless oil): MS *m*/*e* 296 (M^+); IR (CH_2Cl_2) 3590, 3302, 2960, 2931, 2858, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.85 (s, 9H), 0.94 (d, J = 4.8 Hz, 3H), 0.96 (d, J = 4.2 Hz, 3H), 1.53 (s, 1H), 1.81 (s, 3H), 2.23−2.41 (m, 2H), 2.43 (s, 1H), 2.72−2.86 (m, 1H), 3.46−3.67 (m, 2H), 5.25 (s, 1H). **Enynone 1w**: R_f 0.64 (silica gel, 10% EtOAc/hexanes); MS *m*/*e* 279 (M^+ − 15 [CH_3]); IR (CH_2Cl_2) 3293, 2924, 2857, 2093, 1688, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.08 (d, J = 12.0 Hz, 6H),

2.08 (s, 3H), 2.68 (t, J = 10.5 Hz, 2H), 2.82–2.94 (m,1H), 3.29 (s, 1H), 3.67 (t, J = 10.5 Hz, 2H).

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methyl-5-methylene-3-(1-methylethyl)-2-cyclopenten-1-one (7w). This material was prepared in 74% yield from enynone **1w** using method H described above (8 h). Purification by chromatography (silica gel, 5% EtOAc/hexanes) afforded **7w** as a pale yellow oil: R_f 0.32 (silica gel, 10% EtOAc/hexanes); MS m/e 279 (M^+ − 15 [CH_3]); IR (CH_2Cl_2) 3303, 3251 2959, 2879, 2090, 1658, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.81 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.61 (s, 3H), 2.88–3.00 (m, 1H), 3.33 (br, 1H), 3.63 (dd, J = 4.2, 5.6 Hz, 1H), 3.91 (dd, J = 2.8, 5.6 Hz, 1H), 5.39 (s, 1H), 6.01 (s, 1H).

4-(Hydroxymethyl)-2-methyl-5-methylene-3-(1-methylethyl)-2-cyclopenten-1-one (42w). A solution of 120.0 mg (0.41 mmol) of cyclopentenone **7w** in 3 mL of THF was cooled to 0 °C and treated with 4.8 mL of 5% HF/CH_3CN. The reaction mixture was then allowed to warm slowly to rt and stirring was continued for an additional 15–30 min (TLC monitoring). At the end of this period, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and 20 mL of saturated brine. The layers were separated and the aqueous phase was extracted with 3 × 20 mL of Et_2O. The combined organic extracts were washed with 10 mL of saturated $NaHCO_3$ and 15 mL of saturated brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and chromatography (silica gel, 25% acetone/hexanes) then afforded 62.4 mg (84%) of alcohol **42w** as a colorless oil: R_f 0.1 (silica gel, 10% EtOAc/hexanes); MS m/e 180 (M^+); IR (CH_2Cl_2) 3606, 3476, 2932, 2878, 1694, 1652, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 7.20 Hz, 3H), 1.28 (d, J = 7.2, 3H), 1.87 (s, 3H), 2.95–3.06 (m, 1H), 3.46 (br s, 1H), 3.72–3.83 (m, 1H), 4.02–4.13 (m, 1H), 5.49 (s, 1H), 6.14 (s, 1H).

3-Methyl-5-methylene-2-(1-methylethyl)-4-oxo-2-cyclopentene-1-carboxylic Acid, Methyl Ester (44w). A solution of 62.4 mg (0.35 mmol) of alcohol **42w** in 12 mL of acetone was cooled to 0 °C and treated with 0.22 mL (1.75 mmol, 5.00 equiv) of freshly prepared 8.00 M Jones reagent. After addition was complete, stirring was continued at 0 °C for 45 min and the reaction mixture was then extracted with 3 × 5 mL of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to afford the crude carboxylic acid **43w**, which was dissolved in 5 mL of Et_2O and esterified by dropwise addition of a solution of CH_2N_2/Et_2O. The esterification was closely monitored by TLC to ensure that the acid was not treated with excess CH_2N_2. After all **43w** had reacted, the Et_2O was removed under reduced pressure and the crude product was chromatographed (silica gel, 15% acetone/hexanes) to afford 54.4 mg (75%) of methyl ester **44w** as a pale yellow oil, which had spectral data indentical with those of an authentic sample:[7d,24a] MS m/e 208 (M^+); IR (CH_2Cl_2) 2928, 2877, 1738, 1694, 1658, 1622, 1470, 1192, 1164, 1100, 1032, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, J = 6.9, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.88 (d, J = 1.5 Hz, 3H), 2.94–3.11 (m, 1H), 3.70 (s, 3H), 4.21 (s, 1H), 5.49 (d, J = 1.2 Hz, 1H), 6.12 (d, J = 1.2 Hz, 1H); exact mass calcd for ($C_{12}H_{16}O_3$ + H) 209.1178, found 209.1178.

5,6-Dihydro-2,3-dimethyl-2*H*-pyran-2-one (38x).[18,23] This material was prepared in 43% yield from 5.98 g (52.5 mmol) of 2,3-dimethyl-3-butenoic acid (**36x**)[22] by an identical procedure to that described above for pyrone **38w**. Purification by chromatography (silica gel, 25% EtOAc/hexanes) afforded 2.84 g of **38x** as pale yellow oil: MS m/e 126 (M^+); IR (neat) 2979, 2932, 2885, 1702, 1649, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 1.95 (s, 3H), 2.39 (t, J = 5.4 Hz, 2H), 4.30 (t, J = 6.0 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.5, 20.5, 30.5, 65.3, 122, 150, 166.

(*Z*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,3-dimethyl-2-pentenoic Acid, Methyl Ester (46x). A mixture of 3.80 g (30.2 mmol, 1.00 equiv) of lactone **38x** and 2.03 g (36.2 mmol, 1.20 equiv) of KOH in 30 mL of H_2O was heated at reflux for 1 h. At the end of this period, the H_2O was removed under reduced pressure and the residue was dried under high vacuum overnight. The dried potassium salt was then dissolved in 30 mL of anhydrous DMF and treated with 7.20 mL (116 mmol, 3.83 equiv) of CH_3I. The resulting mixture was stirred at rt for 24 h and was then poured into a mixture of ice/water. The aqueous solution was extracted with 3 × 30 mL of Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield methyl (*Z*)-5-hydroxy-2,3-dimethyl-2-pentenoate (**45x**) as a yellow oil which was utilized without purification. This last material was immmediately silylated by being dissolved in 38.0 mL of CH_2Cl_2 and treated sequentially with 3.90 mL (28.0 mmol) of Et_3N, 4.69 g (30.5 mmol) of *tert*-butyldimethylsilyl chloride (TBDMSiCl), and 0.41 g (3.36 mmol) of (*N*,*N*-dimethylamino)pyridine (DMAP) at 0 °C. After stirring for 10 min, the reaction mixture was allowed to warm to rt and stirring was continued for an additional 2 h. At the end of this period, the mixture was diluted with 50 mL of Et_2O and was washed with 20 mL of 1.0 M aqueous HCl and 30.0 mL of saturated brine. The Et_2O layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue was chromatographed (silica gel, 3% EtOAc/hexanes) to afford 6.08 g (73%) of **46x** as a colorless oil: R_f 0.84 (silica gel, 10% EtOAc/hexanes); MS m/e 241 (M^+ − 31 [OCH_3]); IR (neat) 2955, 2931 2884, 2861, 1708, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 1.82 (br s, 6H), 2.60 (t, J = 7.2 Hz, 2H), 3.68 (s, 3H), 3.73 (t, J = 5.6 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.5, 19.0, 22.0, 27.0, 40.3, 51.8, 63.0, 124, 145, 170.

(*Z*)-2,3-Dimethyl-5-[(tetrahydropyran-2-yl)oxy]-2-pentenoic Acid, Methyl Ester (46y). A solution of 0.19 g (1.21 mmol, 1.00 equiv) of crude methyl (*Z*)-5-hydroxy-2,3-dimethyl-2-pentenoate (**45x**), prepared as described above, in 4 mL of CH_2Cl_2 was treated with 0.55 mL (6.05 mmol, 5.00 equiv) of 3,4-dihydro-2*H*-pyran and 30.3 mg (0.12 mmol, 0.10 equiv) of pyridinium *p*-toluenesulfonate (PPTS) at rt. After stirring at rt for 6.5 h, the reaction mixture was concentrated under reduced pressure and the residue was taken up in 10 mL of Et_2O. The ethereal solution was then washed with 10 mL of saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography (silica gel, 25% EtOAc/hexanes) then afforded 0.22 g (78%) of **46y** as a colorless oil: R_f 0.45 (silica gel, 25% EtOAc/hexanes); MS m/e 212 (M^+ − 30 [C_2H_6]); IR (CH_2Cl_2) 2926, 2872, 1711, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38–1.49 (m, 6H), 1.69 (s, 6H), 2.54–2.57 (m, 2H), 3.34–3.42 (m, 2H), 3.59 (s, 3H), 3.66–3.72 (m, 2H), 4.47 (br s, 1H).

(*Z*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,3-dimethyl-2-penten-1-ol (47x). This material was prepared in 72% yield by LAH reduction of 4.01 g (14.5 mmol) of ester **46x** following the general procedure described above for the preparation of diol **39w**. Purification by chromatography (silica gel, 12% EtOAc/hexanes) gave 2.60 g of alcohol **47x** as a colorless oil: R_f 0.32 (silica gel, 12% EtOAc/hexanes); MS m/e 187 (M^+ − 57 [C_4H_9]); IR (CH_2Cl_2) 3601, 3436, 2919, 2861, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.66 (s, 3H), 1.77 (s, 3H), 2.35 (t, J = 6.0 Hz, 2H), 3.66 (t, J = 6.0 Hz, 2H), 3.98 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.0, 19.5, 26.5, 37.5, 61.3, 64.0, 130, 133.

(*Z*)-2,3-Dimethyl-5-[(tetrahydropyran-2-yl)oxy]-2-penten-1-ol (47y). This material was prepared in 74% yield by LAH reduction of 0.78 g (3.24 mmol) of ester **46y** following the general procedure described above for the preparation of diol **39w**. Purification by chromatography (silica gel, 25% EtOAc/hexanes) afforded 0.51 g of **40y** as a colorless oil: R_f 0.23 (25% EtOAc/hexanes); MS m/e 196 (M^+ − 18 [H_2O]); IR (CH_2Cl_2) 3604, 3466, 2923, 2877, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50–1.61 (m, 6H), 1.72 (s, 3H), 1.81 (s, 3H), 2.35–2.46 (m, 2H), 3.38–3.53 (m, 2H), 3.76–3.90 (m, 2H), 4.03 (s, 2H), 4.62 (br s, 1H).

(*Z*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,3-dimethyl-2-pentenal (48x). This material was prepared in 93% yield by MnO_2 oxidation of 2.51 g (10.1 mmol) of alcohol **47x** following the general procedure described above for aldehydes **11c–e**. Purification by chromatography (silica gel, 5% EtOAc/hexanes) afforded 2.32 g of **48x** as a colorless oil: R_f 0.65 (silica gel, 10% EtOAc/hexanes); MS m/e 225 (M^+ − 15 [CH_3]); IR (CH_2Cl_2) 2990, 2931, 2861, 2684, 1661, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.85 (s, 9H),

1.75 (s, 3H), 1.97 (s, 3H), 2.49 (t, J = 7.5 Hz, 2H), 3.74 (t, J = 7.5 Hz, 2H), 10.07 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.5, 18.8, 22.5, 26.5, 36.5, 62.0, 135, 155, 192.

(*Z*)-2,3-Dimethyl-5-[(tetrahydropyran-2-yl)oxy]-2-pentenal (48y). This material was prepared in 97% yield by MnO_2 oxidation of 0.38 g (1.78 mmol) of alcohol **47y** following the general procedure described above for aldehydes **11c–e**. Purification by chromatography (silica gel, 10% EtOAc/hexanes) afforded 0.37 g of **48y** as colorless oil: R_f 0.44 (silica gel, 25% EtOAc/hexanes); MS m/e 197 (M^+ − 15 [CH_3]); IR (CH_2Cl_2) 2927, 2877, 1725, 1665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.61 (m, 6H), 1.78 (s, 3H), 2.00 (s, 3H), 2.85 (m, 2H), 3.50–3.59 (m, 2H), 3.71–3.92 (m, 2H), 4.60 (br s, 1H), 10.10 (s, 1H).

(*Z*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4-dimethyl-3-hepten-6-yn-5-one (1x). This material was prepared in 46% yield from aldehyde **48x** and acetylene **12a** following method A described above. **Intermediate acetylenic alcohol 49x** (colorless oil): R_f 0.32 (10% EtOAc/hexanes); MS m/e 211 (M^+ − 57 [C_4H_9]); IR (CH_2Cl_2) 3406, 3306, 2929, 1664, 1643, 1462, 1079, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.72 (s, 3H), 1.87 (s, 3H), 2.28–2.36 (m, 1H), 2.48 (s, 1H), 2.50–2.58 (m, 1H), 3.12 (s, 1H), 3.62–3.76 (m, 2H), 5.28 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.9, 18.9, 19.4, 26.0, 61.0, 62.0, 73.3, 84.0, 130, 131. **Enynone 1x** (pale yellow oil): R_f 0.67 (silica gel, 10% EtOAc/hexanes); MS m/e 221 (M^+ − 45 [C_3H_9]); IR (neat) 3295, 2919, 2861, 2085, 1649, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.92 (s, 3H), 2.02 (s, 3H), 2.74 (t, J = 6.7 Hz, 2H), 3.26 (s, 1H), 3.77 (t, J = 6.7 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.6, 19.0, 23.8, 26.6, 40.0, 63.2, 80.0, 83.3, 132, 151, 180; exact mass calcd for ($C_{15}H_{26}O_2Si$ + H) 267.1780, found 267.1772.

(*Z*)-3,4-Dimethyl-1-[(tetrahydropyran-2-yl)oxy]-3-hepten-6-yn-5-one (1y). This material was prepared in 40% yield from aldehyde **48y** and acetylene **12a** following method A described above. **Intermediate acetylenic alcohol 49y** (colorless oil): R_f 0.33 (25% EtOAc/hexanes); MS m/e 220 (M^+ − 18 [H_2O]); IR (CH_2Cl_2) 3420, 2947, 2876, 2242, 1793 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.59 (m, 6H), 1.73 (s, 3H), 1.87 (s, 3H), 2.24–2.33 (m, 1H), 2.48 (s, 1H), 2.63–2.72 (m, 1H), 2.90 (br s, 1H), 3.34–3.54 (m, 2H), 3.55–3.92 (m, 2H), 4.60 (br s, 1H), 5.36 (s, 1H). **Enynone 1y** (pale yellow oil): R_f 0.34 (10% EtOAc/hexanes); MS m/e 151 (M^+ − 85 [C_5H_9O]); IR (CH_2Cl_2) 3299, 2945, 2872, 2094, 1650, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49–1.60 (m, 6H), 1.94 (s, 3H), 2.02 (s, 3H), 2.84 (t, J = 6.3 Hz, 2H), 3.28 (s, 1H), 3.47–3.61 (m, 2H), 3.81–3.91 (m, 2H), 4.62 (br s, 1H).

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2,3-dimethyl-5-methylene-2-cyclopenten-1-one (7x). This material was prepared in 84% yield from enynone **1x** using method H described above (11 h). Purification by chromatography (silica gel, 10% EtOAc/hexanes) afforded **7x** as a pale yellow oil: R_f 0.52 (16% EtOAc/hexanes); MS m/e 236 (M^+ − 30 [C_2H_6]); IR (CH_2Cl_2) 2951, 2934, 2861, 1684, 1655, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.79 (s, 3H), 2.09 (s, 3H), 3.23 (br m, 1H), 3.75 (dd, J = 2.8, 5.6 Hz, 1H), 3.82 (dd, J = 4.0, 5.2 Hz, 1H), 5.42 (s, 1H), 6.06 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 9.00, 16.0, 18.9, 26.3, 50.0, 64.8, 116, 140, 145, 166; exact mass calcd for ($C_{15}H_{26}O_2Si$ + H) 267.1780, found 267.1773.

2,3-Dimethyl-5-methylene-4-[[(tetrahydropyran-2-yl)oxy]methyl]-2-cyclopenten-1-one (7y). This material was prepared in 64% yield from enynone **1y** using method H described above (11 h). Purification by chromatography (silica gel, 15% EtOAc/hexanes) afforded **7y** as a pale yellow oil, which had identical spectral data identical with those of an authentic sample:[7d,25a] MS m/e 206 (M^+ − 30 [C_2H_6]); IR (CH_2Cl_2) 2921, 2871, 1691, 1631, 1386, 1122, 1076, 1035, 869 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.72 (m, 6H), 1.75 (s, 3H), 2.08 (s, 3H), 3.33–3.57 (m, 3H), 3.71–3.85 (m, 1H), 3.96 (dd, J = 3.8, 5.1 Hz, 1H), 4.57 (s, 1H), 5.45 (d, J = 5.1 Hz, 1H), 6.03 (d, J = 6.4 Hz, 1H); exact mass calcd for $C_{13}H_{20}O_3$ 235.1332, found 235.1334.

4-(Hydroxymethyl)-2,3-dimethyl-5-methylene-2-cyclopenten-1-one (50). This material was prepared in 92% yield by HF-catalyzed deprotection of 64.1 mg (0.24 mmol) of silyl derivative **7x** following an analogous procedure to that described above for the preparation of alcohol **42w**. Purification by chromatography (silica gel, 25% acetone/hexanes) afforded 33.9 mg of cyclopentenone **50** as a colorless oil: MS m/e 122 (M^+ − 30 [C_2H_6]); IR (CH_2Cl_2) 3450, 3080, 2940, 1690, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.13 (s, 3H), 3.28 (br, 1H), 3.88 (dd, J = 4.0, 5.0 Hz, 1H), 4.00 (dd, J = 4.0, 7.0 Hz, 1H), 5.48 (s, 1H), 6.13 (s, 1H); exact mass calcd for ($C_9H_{12}O_2$ + H) 153.0916, found 153.0913.

2,3-Dimethyl-5-methylene-4-oxo-2-cyclopentene-1-carboxylic Acid (7z) [Desepoxy-4,5-didehydromethylenomycin A]. A solution of 34.3 mg (0.23 mmol) of alcohol **50** in 3 mL of acetone was cooled to 0 °C and treated with 0.14 mL (1.15 mmol, 5.00 equiv) of freshly prepared 8.00 M Jones reagent. After addition was complete, stirring was continued at 0 °C for 45 min and the reaction mixture was then extracted with 3 × 5 mL of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, concentrated, and chromatographed (silica gel, 25% acetone/ hexanes + 1% of AcOH) to afford 29.3 mg (78%) of **7z** as a colorless oil, which had spectral data identical with those of an authentic sample:[7d,26a] MS m/e 122 (M^+ − 44 [CO_2]); IR (CH_2Cl_2) 3502, 3182, 3028, 2925, 2856, 1698, 1632, 1414, 1333, 1258, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.14 (s, 3H), 4.10 (br s, 1H), 5.65 (s, 1H), 6.21 (s, 1H); exact mass calcd for $C_9H_{10}O_3$ 166.0632, found 166.0630.

Acknowledgment. Financial support of this work by the National Science Foundation, Grant No. CHE-9001485, is gratefully acknowledged.

Supplementary Material Available: Copies of NMR spectra for compounds **11c–e**, **18h–i**, **1a–y**, **7a–e** (**Z** and **E**), **7j–q** (**Z** and **E**), **7w–z**, **26**, **27**, **33w**, **36w**, **38 w,x**, **39w**, **42w**, **44w**, **46x,y**, **47x,y**, **48x,y**, and **50** (84 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.